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Development of Sustainable Catalytic Systems For Oxidation Reactions

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Development of Sustainable Catalytic Systems for Oxidation Reactions

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A Thesis Submitted for the Degree of Doctor of Philosophy

at the

School of Chemistry and Chemical Engineering

Queen's University of Belfast



12th April 2017

Supervisor: Dr Mark J. Muldoon

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List of Abbreviations

ABNO – 9-azabicyclo[3.3.1] nonane *N*-oxyl

AcOH - acetic acid

Ar – argon

AZADO – 2-azaadamantane *N*-oxyl

BDE – bond disassociation energy

BET – Brauner Emmett Teller analysis

[bmim] – 1-butyl-3-methylimidazolium

Bu₃N – tributylamine

[C₄mPyr] – 1-butyl-1-methylpyrrolidinium

[C₈mim]- 1-octyl-3-methylimidazolium

[C₈Py] – *N*-octylpyridinium

CDC – cross-dehydrogenative coupling

CH₃SO₃H – methanesulfonic acid

CO- carbon monoxide

CO₂ – carbon dioxide

Co₂(CO)₈ – dicobalt octacarbonyl

Cs₂CO₃ – caesium carbonate

DBU – 1,8-diazobicyclo[5.4.0]undec-7-ene

DCC- *N,N'*-dicyclohexylcarbodiimide

DCE - dichloroethane

DCM – dichloromethane

DEF – *N,N'*-diethylformamide

DIEA –diisopropylethylamine

DMA – dimethylacetamide

DMAP – 4-(dimethylamino)pyridine

DMF – *N*-dimethylformamide

DMSO - dimethylsulfoxide

DNA-PK – Dioxynucleic acid (DNA) protein kinase

Dppb- 1,4-bis(diphenylphosphino)butane

DRIFT – diffuse reflectance infrared fourier transform

EDCI – 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

EI - electron ionisation

EPR – electron paramagnetic resonance

ESI-MS - electrospray mass spectrometry

Et₃N – triethylamine

ETM- electron transfer mediator

EtOAc- ethyl acetate

[FAP] – tris(pentafluoroethyl)trifluorophosphate

GC – gas chromatography

H₂BIP – 2,6-bis(benzimidazol-2'-yl)pyridine

HSA –8-hydroxyquinoline-2-sulfonic acid

HCOOH – formic acid

HOBt – hydroxybenzotriazole

HOCl – hypochlorous acid

HPLC – high performance liquid chromatography

IAMN – isoamyl nitrite

ICP- inductively coupled plasma atomic emission spectroscopy

IOAc – iodine acetate

IL – ionic liquid

IR –infrared

K₂CO₃ – potassium carbonate

K₃PO₄ – potassium phosphate

ketoABNO – 9-azabicyclo[3.3.1]nonane-3-one *N*-oxyl

KI – potassium iodide

LDA – lithium diisopropylamide

LFL - lower flammability limit

LiO^tBu – lithium *tert*-butoxide

LOC - limiting oxygen concentration

1-Me-AZADO – 1-methyl-2-azaadamantane N-oxyl

MeCN- acetonitrile

Me₂S – dimethyl sulfide

MnO₂ – manganese dioxide

MS - molecular sieves

MTES – methyltriethoxysilane

MW – microwave

NACOS – nitric acid assisted carbon catalysed oxidation system

NaHCO₃ – sodium hydrogencarbonate

NaI – sodium iodide

n-BuLi - *n*-butyllithium

[N₂₂₂₈] – triethyloctylammonium

[NBu₄][Br] – tetrabutylammonium bromide

[NBu₄][Cl] – tetrabutylammonium chloride

[NBu₄][I] – tetrabutylammonium iodide

[NBu₄][IO] – tetrabutylammonium hypoiodite

[NBu₄][IO₂] – tetrabutylammonium iodite

[NBu₄][OAc] –tetrabutylammonium acetate

[NBu₄][OH] –tetrabutylammonium hydroxide

[NTf₂] – bistriflimide

NHC – *N*-heterocyclic carbene

NHPI – *N*-hydroxyphthalimide

NMDA- *N*-methyl-D-aspartate

NMI - *N*-methylimidazole

NMO – *N*-methylmorpholine-*N*-oxide

NMR – nuclear magnetic resonance

PAR – protease activated receptor

PDE-5 – phosphodiesterase

PET – polyethylene terephthalate

[PF₆] – hexafluorophosphate

Phen – phenanthroline

PINO – phthalimide-*N*-oxyl

POM – polyoxometalate

RT- room temperature

SILP – supported ionic liquid phase catalyst

SQUID – superconducting quantum interference device

TBHP- *tert*-butyl hydrogen peroxide

TBN – *tert*-butyl nitrite

TBSO – *tert*-butyldimethylsilyl

TEG – triethylene glycol

TEM- transmission electron spectroscopy

TEMPO - 2,2,6,6-tetramethylpiperidine-*N*-oxyl

TGA – thermal gas analysis

THF- tetrahydrofuran

TMEDA – N',N',N', N'-tetramethylethylenediamine

TPAP – tetrapropylammonium perruthenate

UFL- upper flammability limit

UHP- urea hydrogen peroxide

UV- ultraviolet

UV- Vis –ultraviolet-visible

Xphos – (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl)

Abstract

Oxidations are a fundamental class of reactions in organic chemistry. Furthermore, the ability to carry out such transformations in an efficient and selective manner has the potential for widespread application in the production of both bulk and fine chemicals, pharmaceuticals, agrochemicals and many more. Despite this, oxidations are often avoided due to the environmental and economic problems associated with traditional, stoichiometric oxidising agents.

Within this thesis, three methods for the aerobic catalytic preparation of carbonyl compounds will be studied. This is done with the aim to develop sustainable methods for aerobic catalytic oxidation reactions that may help in the efforts to use aerobic catalysis on an industrial scale.

Chapter two focusses on the development of a metal-free aerobic catalytic system for alcohol oxidation using sterically unhindered nitroxyl radicals in combination with nitric acid. The aim is to broaden the substrate scope of the reaction, whilst using a cheap, abundant source of NO_x .

Chapter three explores the use of Pd(II) catalysed oxidative carbonylation for the synthesis of 2-alkynoates. The focus is to use lower catalyst loadings than previously reported through the use of ligands, whilst improving the selectivity and substrate scope of the reaction.

Chapter four studies Pd(II) catalysed aminocarbonylation for the synthesis of 2-ynamides. This system employs a greener solvent, and operates under safer reaction conditions than existing literature, yet maintains equal efficiency and substrate versatility.

Contents Page

Chapter 1: Introduction to Oxidations	1
1.1 Oxidations	1
1.2 Traditional Oxidants	1
1.3 Molecular Oxygen as an Oxidant	3
1.4 Project Aims	5
1.5 References	7
Chapter 2: Metal-Free Aerobic Catalytic Alcohol Oxidation	8
2.1 Introduction	8
2.1.1 Alcohol Oxidation	8
2.1.2 Sterically Unhindered Nitroxyl Radicals	11
2.1.3 Metal-Free Aerobic Alcohol Oxidation <i>via in situ</i> formation of <i>N</i> -Oxoammonium Salts	20
2.1.4 Immobilisation of Radicals in Transition Metal-Free Aerobic Oxidations of Alcohols <i>via in situ</i> formation of <i>N</i> -Oxoammonium salts	28
2.1.4.1 <i>Radical Recycling via Immobilisation onto Silica</i>	29
2.1.4.2 <i>Radical Recycling via Ionic Liquids</i>	32
2.1.4.3 <i>Radical Recycling via SILPS</i>	35
2.1.4.4 <i>Radical Recycling via Phase Separation</i>	37
2.2 Aims and Objectives	39
2.3 Results and Discussion	40
2.4 Conclusion	64
2.5 Experimental	66
2.5.1 General Considerations	66
2.5.2 General Methods	68
2.5.3 Synthesis of Ionic Liquids	67
2.5.4 Synthesis of SILPS	70
2.5.5 Synthesis of Covalently Tethered TEMPO	73
2.5.6 Synthesis of Nitroxyl Radicals	75
2.5.7 Spectra	80

2.6 References	85
 Chapter 3: Palladium(II) Catalysed Oxidative Carbonylation of Terminal Alkynes for the Synthesis of 2-Alkynoates	88
3.1 Introduction	88
3.1.1 Importance of 2-Alkynoate Synthesis	88
3.1.2 Traditional Synthesis of 2-Alkynoates	91
3.1.3 Catalytic Carboxylative Coupling with CO ₂ for the Synthesis of 2-Alkynoates	92
3.1.4 Palladium(II) Catalysed Oxidative Carbonylation for the Synthesis of 2-Alkynoates	96
3.2 Aims and Objectives	107
3.3 Results and Discussion	108
3.4 Conclusion	122
3.5 Experimental	124
3.5.1 General Considerations	124
3.5.2 Safety Considerations	126
3.5.3 General Methods	126
3.5.4 Analysis of Pd(OAc) ₂	128
3.5.5 Synthesis of Isolated (Phen)Pd(OAc) ₂ Complex Applied in CO ₂ Testing Reactions	130
3.5.6 Product Characterisation	131
3.5.7 NMR Spectra	140
3.5.8 Example IR Spectra	160
3.6 References	161
 Chapter 4: Palladium(II) Catalysed Aminocarbonylation of Terminal Alkynes for the Synthesis of 2-Ynamides	164
4.1 Introduction	164
4.1.1 Importance of 2-Ynamide Synthesis	164
4.1.2 Non-Catalytic Approaches for the Synthesis of 2-Ynamides	166
4.1.3 Catalytic Approaches for the Synthesis of 2-Ynamides	167

4.1.4 Catalytic Approaches to 2-Ynamide Synthesis Utilising Oxygen or Air as the Terminal Oxidant	172
4.2 Aims	183
4.3 Results and Discussion	184
4.4 Conclusion	207
4.5 Experimental	208
4.5.1 General Considerations	208
4.5.2 Safety Considerations	209
4.5.3 General Methods	210
4.5.4 Product Characterisation	211
4.5.5 Synthesis of Iodoethynylbenzene	218
4.5.6 NMR Spectra	219
4.5.7 Example IR Spectra	234
4.6 References	235
 Conclusions and Further Work	 238
 Appendix of Selected Publications	 239

Chapter 1

Introduction to Oxidations

1.1 Oxidations

The oxidation of organic molecules is a diverse area of chemistry with potential widespread applications in a large number of fine and speciality chemicals manufacture, such as in the production of pharmaceuticals, and agrochemicals.¹ However, despite the importance of this transformation, oxidations remain problematic on an industrial scale, and in many cases, remain avoided. In a review regarding the types of reactions used for the preparation of drug candidate molecules by three leading pharmaceutical companies (GlaxoSmithKline, Pfizer and AstraZeneca), it was highlighted that only 3.9% of the reactions reviewed were oxidations.² Of these, the highest was sulfur oxidation, followed closely by alcohol oxidation. The industry's reluctance to carry out oxidations is a result of the many problems associated with traditional oxidation methods, such as poor atom efficiency, and the production of large quantities of hazardous waste.

1.2 Traditional Oxidants

Traditionally oxidative transformations are performed using stoichiometric reagents that have been developed to accomplish the transformation in an efficient and selective manner.³ A commonly employed oxidant is chromium(VI) oxide, such as that applied in the preparation of α -amino aldehydes in the presence of pyridine.⁴ (Figure 1.1)

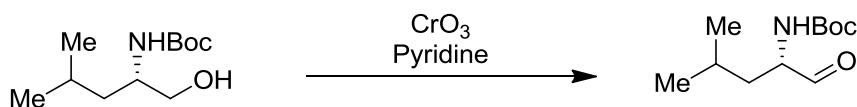


Figure 1.1 Preparation of α -amino aldehydes with CrO_3 in the presence of pyridine.

Problems arise when considering the work-up of the example shown in Figure 1.1. The first step in the work up process to obtain the product, would generally

be a water quench which would generate the product, but result in even larger volumes of chromium and acidic waste which must be treated appropriately prior to disposal.¹ This process is therefore not atom efficient, not to mention the concern that the product may be contaminated with chromium waste. Other transition metals have been employed within the pharmaceutical industry, including manganese dioxide (MnO_2)⁵ or tetrapropylammonium perruthenate (TPAP)⁶. Examples of these reactions can be seen in Figure 1.2.⁷

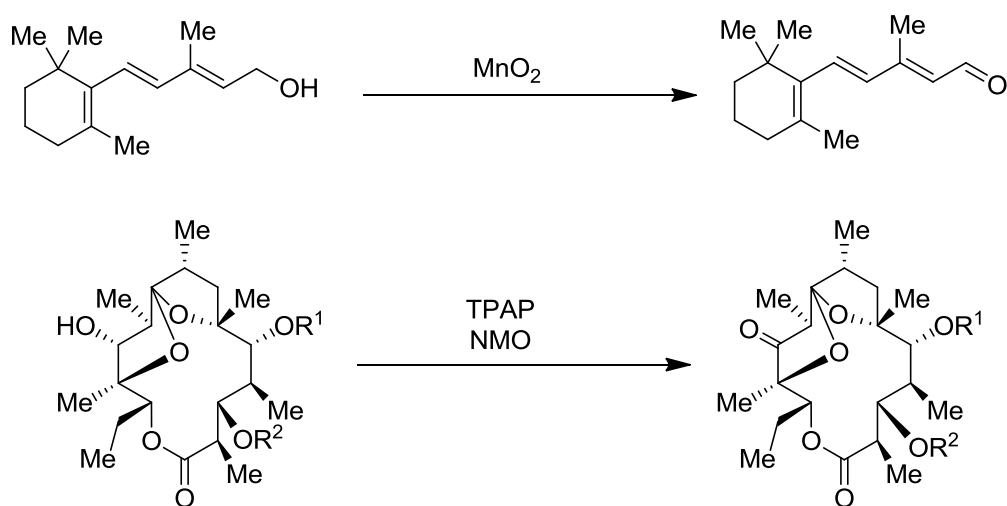


Figure 1.2 Examples of other stoichiometric oxidations.

The example employing MnO_2 is used to prepare an intermediate in the synthesis of isotretinoin, used for the treatment of acne. Despite giving >95% yield, MnO_2 oxidations are not widely employed on a large scale, as due to the high activity of the reagent, it cannot be applied to sensitive substrates.⁷ In addition, the stoichiometric use of the reagent leads to large quantities of waste. The ruthenium reagent (TPAP) can be used in catalytic amounts, however is usually used in conjunction with NMO (*N*-methylmorpholine-*N*-oxide) as a co-oxidant.

Another commonly employed protocol is the Swern oxidation, used for the oxidation of primary alcohols to aldehydes. This procedure requires the use of dimethylsulfoxide (DMSO) and an activator, traditionally oxalyl chloride. One of the main drawbacks of this method is the quantity of Me_2S , CO_2 and CO produced. In addition, the reaction must be run at -78°C when using oxalyl chloride.⁷ The use of a SO_3 -pyridine complex allows for the reaction to be run

under more desirable conditions, however it still produces dimethyl sulphide which is environmentally hazardous. This method has been employed for aldehyde synthesis on a 190 kg scale, in a multistep synthesis for the production of an HIV protease inhibitor.⁸ (Figure 1.3)

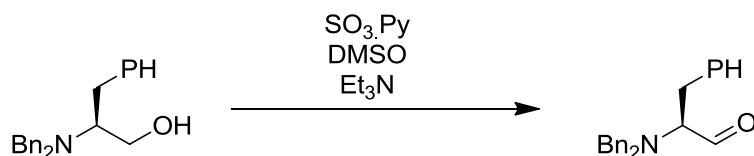


Figure 1.3 Example of modified Swern oxidation.

As can be seen from the examples mentioned, the use of stoichiometric oxidants is not desirable due to the amount of waste produced, poor atom efficiency and the use of hazardous reagents. It would be preferable if the reactions could be performed in a more sustainable, safer manner.

1.3 Molecular Oxygen as an Oxidant

It would be preferable, and perhaps more attractive to industry if oxidations could be performed catalytically, employing molecular oxygen or air as the terminal oxidant. This type of oxidation has several advantages. Firstly oxygen is cheap, abundant and non-toxic. In addition, its sole by-product is water, which is again non-toxic and a stark contrast to the hazardous by-products formed when applying stoichiometric oxidising reagents.

Whereas this environmentally benign protocol of aerobic catalytic oxidation is not yet widely used in pharmaceutical manufacture, it has been used for the production of bulk chemicals. An example is the production of terephthalic acid from *p*-xylene. This is a highly important reaction, as terephthalic acid is then used for the manufacture of many polymers including polyethylene terephthalate (PET). The process is referred to as the Amoco process and involves the transformation of an aldehyde to a carboxylic acid.⁹

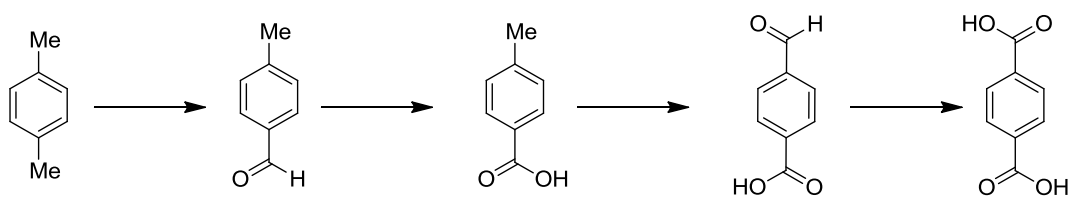


Figure 1.4 Industrial application of oxidation for the synthesis of terephthalic acid.

This process holds many improvements on the previously used manganese dioxide or potassium permanganate/ sodium hydroxide systems, such as improved atom efficiency and a greener solvent. This example suggests that it is possible to move from stoichiometric reagents to catalytic oxidations, and there are benefits to be reaped from doing so.

However, if catalytic oxidations are to be considered for industrial application, many factors must be considered. These include the safety, performance, and economics of the reaction, not to mention the waste produced. This is not an easy task, and so research into oxidative catalysis is very much ongoing, making it an interesting and challenging area to study.

1.4 Project Aims

The focus of this project has been the development of sustainable catalytic systems for oxidation reactions. The project can be split into three main areas.

Chapter two focusses on the development of a metal-free catalytic system for aerobic alcohol oxidation. This system employs the use of nitroxyl radicals in combination with nitric acid for the oxidation of secondary alcohols. In addition several methods are tested for the recycling of the nitroxyl radical in efforts to make the reaction more economically viable for the production of fine chemicals.

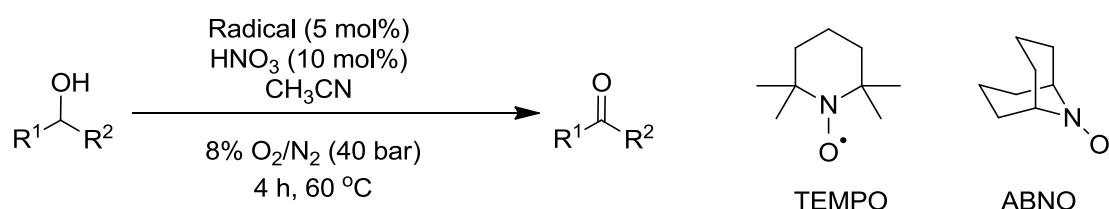


Figure 1.5 Metal-free catalytic aerobic alcohol oxidation.

Chapter three concentrates on palladium(II) catalysed oxidative carbonylation of terminal alkynes for the synthesis of 2-alkynoates. The method developed overcomes many problems associated with previously reported systems, as well as demonstrating a wide substrate scope of both alkynes and alcohols.

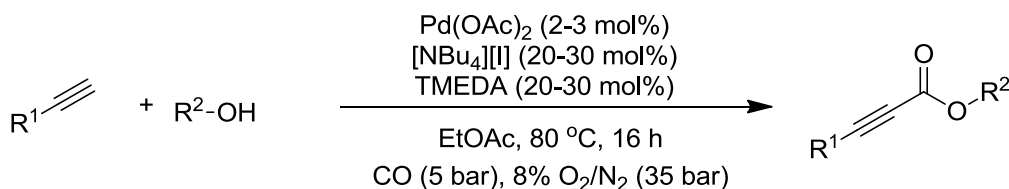


Figure 1.6 Synthesis of 2-alkynoates *via* Pd(II) catalysed oxidative carbonylation.

Part of this chapter is published in Q. Cao, **N. L. Hughes**, and M. J. Muldoon, *Chem. Eur. J.*, 2016, **22**, 11982.

Chapter four studies palladium(II) catalysed aminocarbonylation of terminal alkynes for the synthesis of 2-ynamides. The system developed offers a greener and safer protocol for the synthesis of 2-ynamides.

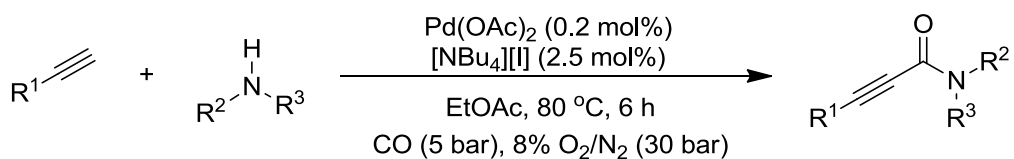


Figure 1.7 Synthesis of 2-ynamides *via* Pd(II) catalysed aminocarbonylation.

Part of this chapter is published in **N. L. Hughes**, C. L. Brown, A. I. Irwin, Q. Cao and M. J. Muldoon, *ChemSusChem*, 2017, **10**, 675.

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Chapter 2

Metal-Free Catalytic Aerobic Alcohol Oxidation

2.1 Introduction

2.1.1 Alcohol Oxidation

The ability to carry out the controlled oxidation of alcohols to their corresponding aldehydes and ketones is one of the most fundamental reactions in organic chemistry.¹ However, despite this, oxidations are rarely performed in the manufacture of the one million tonnes of carbonyl compounds being produced annually worldwide.² These compounds go on to be used in the industrial manufacture of pharmaceuticals, perfumes and food additives.³ The avoidance of oxidations is especially prevalent within the pharmaceutical industry. In an article compiled by industrial experts within the field they highlight that,

“the adjustment of the oxidation state from alcohol to carbonyl is rarely performed even though it is a common feature of many published target- orientated syntheses. The problems associated with many oxidation methods probably means that syntheses requiring them are avoided if possible.”⁴

Traditionally these reactions have been carried out using stoichiometric oxidising agents such as chromium trioxide and Dess Martin Periodinane;⁵ however these have many environmental and economical disadvantages. These reagents produce copious amounts of hazardous waste, generally require the use of halogenated solvents, and the heavy metals involved such as chromium and manganese have a tendency to remain in the final product, even after purification. This is a major disadvantage when considering the use of these processes in pharmaceutical manufacture. Looking at the reaction from a green perspective, it can be thought that these reactions display poor

atom efficiency, as a large amount of waste is generated from a process that only requires the removal of two hydrogen atoms.

With all these factors in mind, a vast amount of work has been carried out in recent years regarding the use of dioxygen in combination with first row transition metals, to facilitate the transformation of alcohols to their corresponding aldehydes and ketones.⁶ This is in relation to comments made by those in the pharmaceutical industry;

“In contrast to reductions, there are relatively few atom efficient, chemoselective and environmentally acceptable oxidation methods. As a consequence, oxidations are often designed out of syntheses. The discovery of new chemoselective oxidations, particularly if catalytic, would greatly increase flexibility in synthetic design.”⁴

From a green perspective, systems utilising dioxygen in combination with first row transition metals are an impressive improvement on the previously used traditional stoichiometric oxidants mentioned earlier, as the generation of waste is greatly minimised, cheap first row transition metals are utilised (such as copper or iron) and the oxidant (dioxygen) is from a renewable source.⁷ In this type of aerobic oxidation system, (that uses dioxygen as the oxidant with a transition metal / nitroxyl radical combination), the metal that has been shown to be most efficient to date is copper.⁸ Many variations on copper containing systems have been reported in the literature,⁹ however one of the most successful is that demonstrated by Hoover and Stahl in 2011. The system comprising of a copper(I) salt, 2,2'-bipyridyl, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), *N*-methylimidazole (NMI), and acetonitrile, can oxidise primary alcohols to their corresponding carbonyl compounds, with high conversions, at room temperature.¹⁰

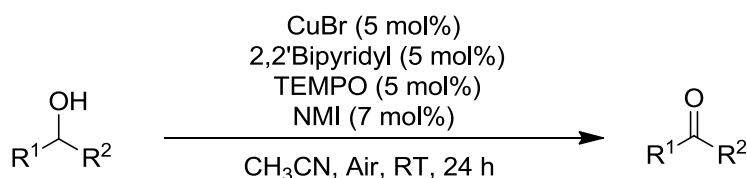


Figure 2.1 Copper(I) / TEMPO catalytic system as proposed by Hoover and Stahl.¹⁰

The system displays a broad substrate scope, with the ability to oxidise primary alcohols with a high selectivity and allow efficient oxidation of aliphatic alcohols that are renowned for being problematic with other aerobic oxidation systems reported in the literature. The system is also heteroatom tolerant, which is a major advantage over previous third row transition metal oxidation systems.¹⁰ However, there are still some limitations; firstly homobenzylic alcohols undergo oxygenation at the benzylic position, to produce an α - ketoaldehyde. In addition, terminal alkynes give a range of unwanted side products. A selection of substrates containing phenols or primary alcohols containing vicinal chelating functionality could not be oxidised, this is thought to be due to their ability to bind strongly through the oxygen or nitrogen respectively to the copper, thus forming an inactive species.¹⁰ Despite a major benefit of the system being the high selectivity exhibited with primary alcohols in the presence of secondary alcohols; it results in the inability to oxidise secondary alcohols, which is also an industrially useful transformation. It is thought that the reason for this is due to the steric hindrance seen in Figure 2.2 between the second alkyl group (R') and the radical moiety, which prevents the formation of the active species.

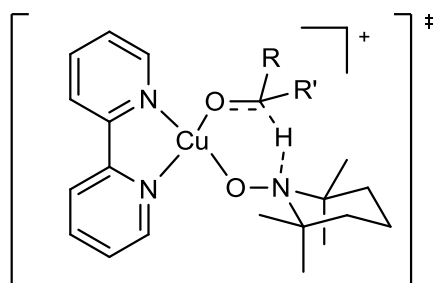


Figure 2.2 Steric hindrance caused by the additional alkyl group on a secondary alcohol when using TEMPO.¹¹

This problem has since been shown to be solved by replacing TEMPO with a less sterically hindered radical such as 9-azabicyclo [3.3.1] nonan-3-one *N*-oxyl (ketoABNO), 9-azabicyclo [3.3.1] nonane *N*-oxyl (ABNO) or 2-azaadamantane *N*-oxyl (AZADO). The difference in transition state when using ABNO can be seen in Figure 2.3. This shows the lack of steric hindrance between the R' group and the radical, which results in the energy of the transition state being lower than when using TEMPO, for both primary and secondary alcohols. This ultimately results in the ability to oxidise secondary alcohol substrates.

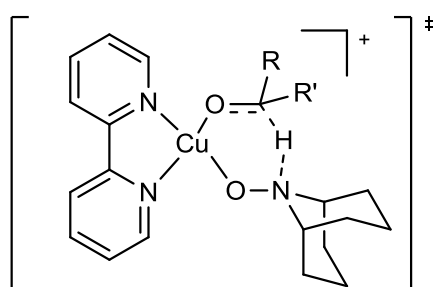


Figure 2.3 Lack of steric hindrance as a result of replacing TEMPO with ABNO.¹¹

2.1.2 Sterically Unhindered Nitroxyl Radicals

In the early 1960's Dupeyre and Rassat isolated a new group of sterically unhindered nitroxyl radicals whereby the nitroxide nitrogen is joined to two bridgehead carbon atoms.¹² Nitroxyl radicals can in some cases, be unstable, as they can disproportionate to give a hydroxylamine and a nitron.¹³ However, in this case, this class of radicals is protected from disproportionation due to Bredt's rules. Bredt's rules state that it is not favourable for a double bond to be positioned at the bridgehead of a bicyclic ring system, with the exception of cases where the ring is large enough. This is due to the large amount of ring and angle strain caused by the orthogonal alignment of the p-orbitals on the bridgehead and adjacent atoms preventing the correct formation of π bonds.¹⁴ Bowry and Ingold reported that this class of radical showed kinetic superiority to that of TEMPO due to the NO moiety in radicals such as ABNO being fully

exposed in contrast to that of TEMPO which is sterically crowded.¹⁵ Despite this being the case, these radicals were not tested for their possible application in alcohol oxidation until a decade ago.

With regards to reactivity this class of sterically unhindered radicals react in a similar manner to TEMPO, whereby the reaction does not proceed *via* an autoxidation reaction. Moreover, TEMPO can in fact act as a radical scavenger, and inhibit such autoxidative reactions. In direct contrast, *N*-hydroxyphthalimide (NHPI) can catalyse autoxidation reactions *via* formation of phthalimide-*N*-oxyl (PINO).¹⁶ The difference in reactivity can be attributed to the difference in bond dissociation energy (BDE) of the O-H bond in the hydroxylamine. The BDE of NHPI is much higher than that of TEMPOH, thus suggesting a higher reactivity of the PINO radical. In the case of TEMPO, hydrogen abstraction would be endothermic, this means that TEMPO will act as a radical scavenger therefore resulting in inhibition of autoxidation.

A selection of these sterically unhindered radicals can be seen in Figure 2.4.

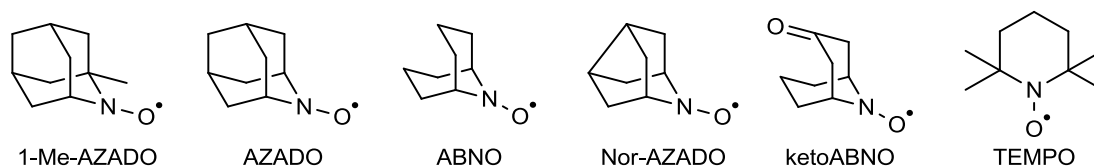


Figure 2.4 Reported *N*-oxyl radicals for the catalytic oxidation of alcohols.

Iwabuchi and co-workers suggested that by using a less hindered class of nitroxyl radical, it would be possible to greatly enhance the scope of aerobic alcohol oxidation.¹⁷ They compared the reactivity of TEMPO and 1-methyl-2-azaadamantane *N*-oxyl (1-Me-AZADO) under Anelli's bleach conditions¹⁸ for the oxidation of 3-phenylpropanol to show that 1-Me-AZADO exhibited a much higher reactivity than that of TEMPO. It should be noted that at catalyst loadings of 0.1 mol%, the yields obtained with the respective radicals were almost identical however when dropped to loadings of 0.001 mol%, the yield of aldehyde was 0% and 62% with TEMPO and 1-Me-AZADO respectively. The report focussed mainly on the oxidation of secondary alcohols, as various

successful methods for the aerobic oxidation of primary alcohols have already been reported in the literature.⁹

It was hypothesised that the remarkable increase in reactivity is due to the lack of steric hindrance on the 1-Me-AZADO radical around the NO moiety, and in order to prove this point, the group synthesised 1,3-dimethylAZADO. This particular radical (Figure 2.5) has steric hindrance around the NO that is similar to that of TEMPO.

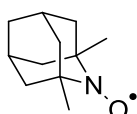


Figure 2.5 Structure of 1, 3-dimethylAZADO.¹⁷

It was shown that 1, 3-dimethylAZADO demonstrated similar reactivity to that of TEMPO when compared for the oxidation of menthol. Menthol is known to be a problematic substrate in terms of aerobic oxidation, due to its bulky structure, and in this case with both TEMPO and 1,3-dimethylAZADO, no oxidation was observed. However, with 1-Me-AZADO, it was possible to produce menthone in a 95 % yield in twenty minutes. This therefore proved that the superior reactivity of this class of radical is a result of kinetic factors that can be related to the decreased steric hindrance at the reaction centre.¹⁷ The main problem with 1-Me-AZADO is that it requires a lengthy six step synthesis.¹⁷ (Figure 2.6)

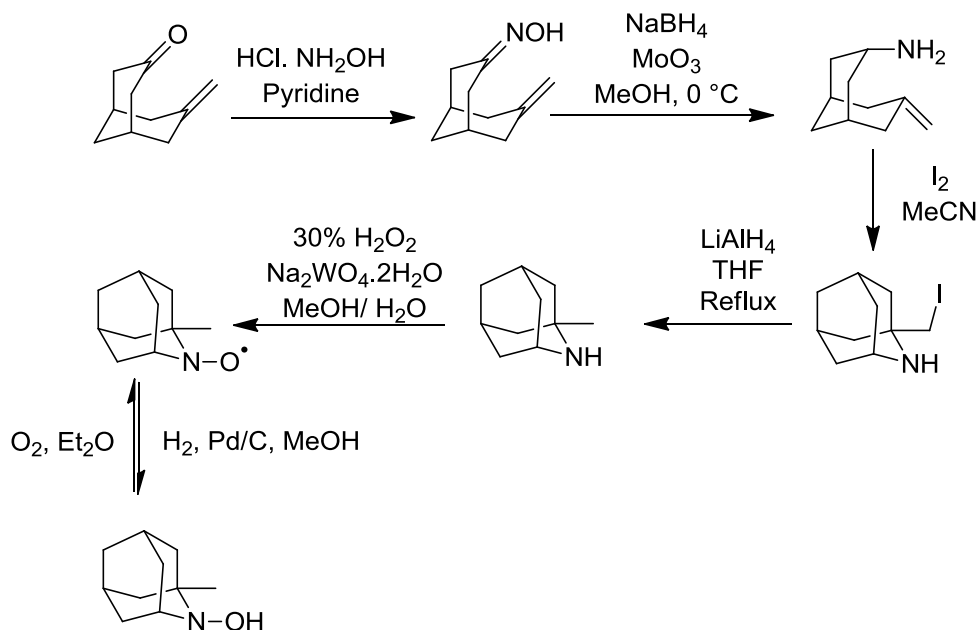


Figure 2.6 Synthesis of 1-Me-AZADO.¹⁷

Due to this, the same group released a follow up paper that showed another similar nitroxyl radical, 9-azabicyclo [3.3.1] nonane *N*-oxyl (ABNO) which could be prepared in only three synthetic steps (Figure 2.7) and exhibited similar reactivity to that reported with 1- Me-AZADO.¹⁹

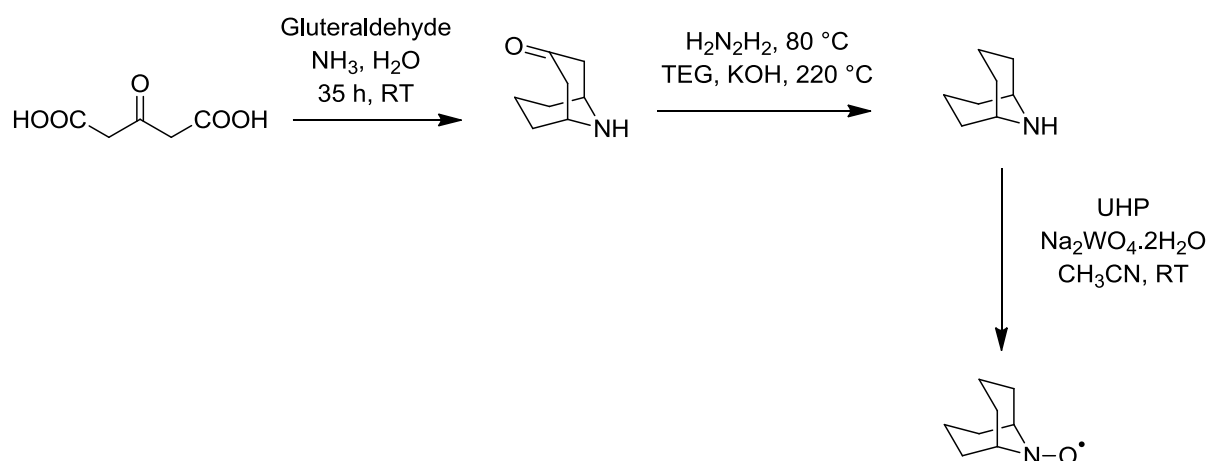


Figure 2.7 Synthesis of ABNO.¹⁹

This method still has some drawbacks, for example in order to carry out the reaction in three steps (without a benzyl protecting group) it is necessary to

use a freeze drier to isolate the ketone intermediate, which is not always accessible. In addition this synthesis requires a Wolff-Kischner reduction step. However, the synthesis is still an overall improvement on the 6-step synthesis required for 1-Me-AZADO.

ABNO was then tested under Anelli's bleach conditions as seen before, to show kinetic superiority over that of TEMPO. Once again, similar reactivity was observed with all three radicals, at catalyst loadings of 0.1 mol%, however when dropped, remarkable differences were observed. At loadings of 0.01 mol% no reaction was observed with TEMPO, yet ABNO and 1-Me-AZADO showed almost identical reactivity. Differences were seen between these two radicals at 0.003 mol%, with 1-Me-AZADO showing higher reactivity, however it should be noted that these results were in short reaction times of one hour or less, and so it may be possible to obtain the same yield with ABNO in a longer time period. Taking this into consideration along with the more simplistic synthesis of ABNO, it is undoubtedly the best choice of radical in this case.

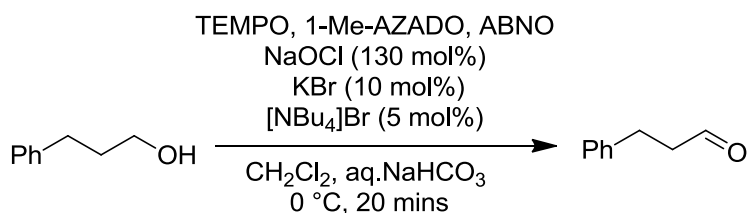


Table 2.1 Comparison of yield obtained when using TEMPO, 1-Me-AZADO and ABNO.¹⁹

Catalyst loading	Yield %	Yield %	Yield %
mol%	TEMPO	1-Me-AZADO	ABNO
1	90	91	90
0.1	88	90	88
0.01	23	91	85
0.003	n.d.	81 (30 mins)	41 (30 mins)
0.001	n.d.	59 (60 mins)	28 (60 mins)

Within the substrate scope (which utilised catalyst loadings of 1 mol% under Anelli's conditions) it was shown that in some cases, ABNO exhibited higher reactivity than that of 1-Me-AZADO. In order to examine this further, the group used a specifically designed bulky secondary alcohol substrate, to closely study the catalytic ability of each radical. The results can be seen in Figure 2.8.

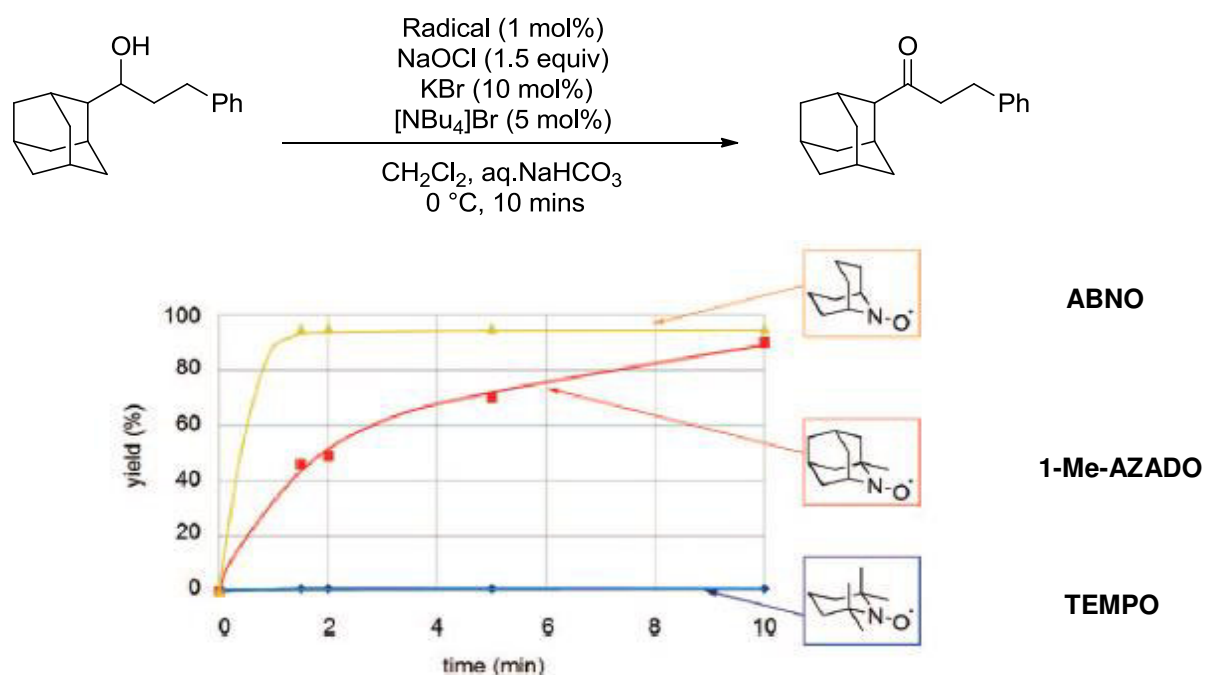


Figure 2.8 Graph to show the difference in reactivity of ABNO, 1-Me-AZADO and TEMPO.¹⁹ Reproduced from reference 19.

From the graph it is possible to see that ABNO consumes the substrate almost immediately, whereas 1-Me-AZADO requires ten minutes to reach the same point. In the case of TEMPO, no reactivity is observed.

More recently, another radical in this class has also been reported for its application in alcohol oxidation, 9-azabicyclo[3.3.1]nonan-2-one (ketoABNO).²⁰ This radical was suspected to have additional enhanced reactivity to those reported previously, as it has an additional electron withdrawing carbonyl group, which should allow for faster single electron oxidation as the species is electron deficient. KetoABNO can also be prepared with three synthetic steps and is arguably more accessible than ABNO, as its

synthesis doesn't involve the potentially explosive Wolf Kishner step, which can cause problems when trying to carry out the synthesis on a large scale.²¹

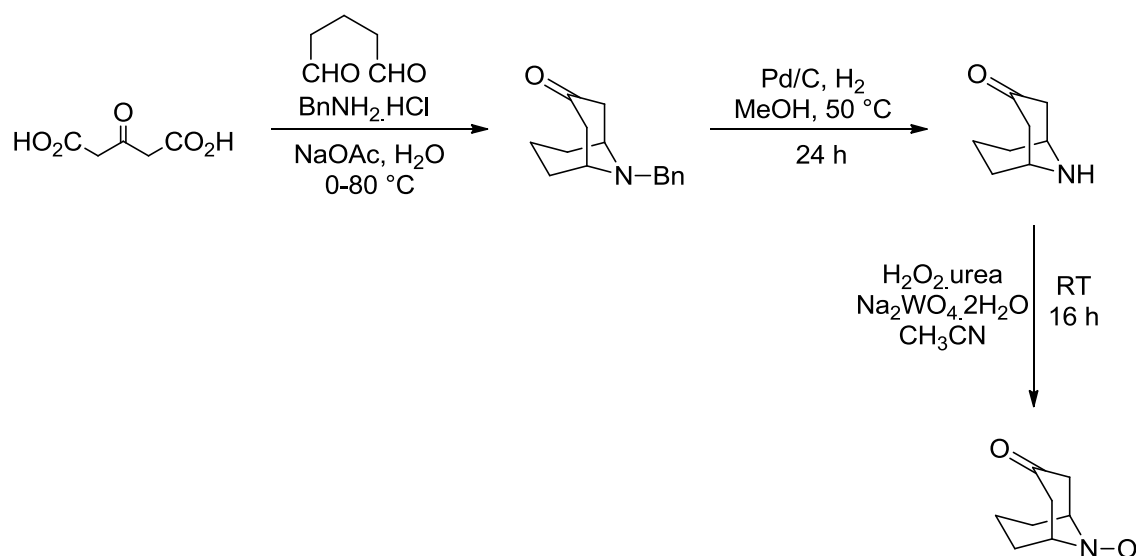


Figure 2.9 Synthesis of ketoABNO.²⁰

In this case, ketoABNO was not utilised for alcohol oxidation, but instead for the copper catalysed aerobic oxidation of amines to imines. The reaction conditions are shown below in Figure 2.10.

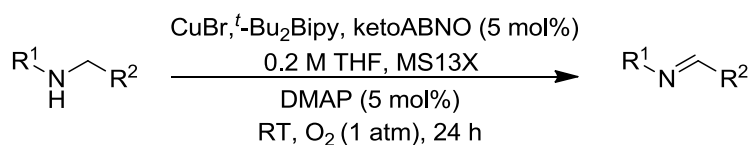


Figure 2.10 Reaction conditions utilising ketoABNO to oxidise amines to imines.²⁰

The reactivity of the system was observed to improve with the addition of molecular sieves, and even more interestingly, the use of ligands with bulky substituents adjacent to the coordinating nitrogen atoms also improved the yields obtained. This is worthwhile mentioning, as it is known with the previously mentioned Cu(I)/TEMPO/ bipyridine system that the addition of bulkier ligands such as neocuprione greatly reduces the catalytic efficiency of the system. However, in this case, the use of bulkier ligands such as *i*Pr-PyBox

and $t\text{-Bu}_2\text{bipy}$ doubled (Figure 2.11), and in some cases tripled the yield of imine obtained. This could be very useful, as the ability to vary the substituents on the ligand could potentially introduce another element of control into the reaction; something that couldn't be done with previous aerobic oxidation copper containing systems.

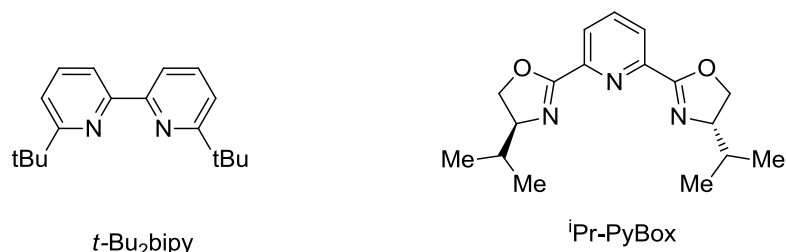


Figure 2.11 Bulky ligands employed for the oxidation of amines to imines.²⁰

The reaction conditions were compared using TEMPO, ABNO, AZADO and ketoABNO, giving imine yields of 14%, 8%, 62% and 80% respectively. Under these conditions it was possible to oxidise both dibenzylamines and N -aryl benzylamines with a high yield at room temperature. Given the high reactivity observed, and the mild reaction conditions the group demonstrated the further synthetic utility of the system by showing the ability to carry out the stepwise addition of a Grignard reagent (Figure 2.12) to oxidatively produce imines and cross dehydrogenative coupling reactions (Figure 2.13).

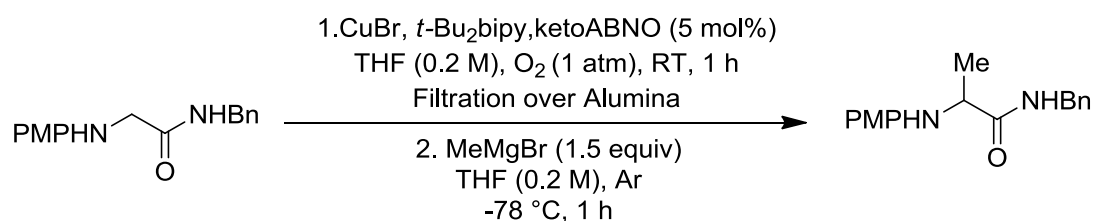


Figure 2.12 Stepwise addition of a Grignard reagent to an imine.²⁰

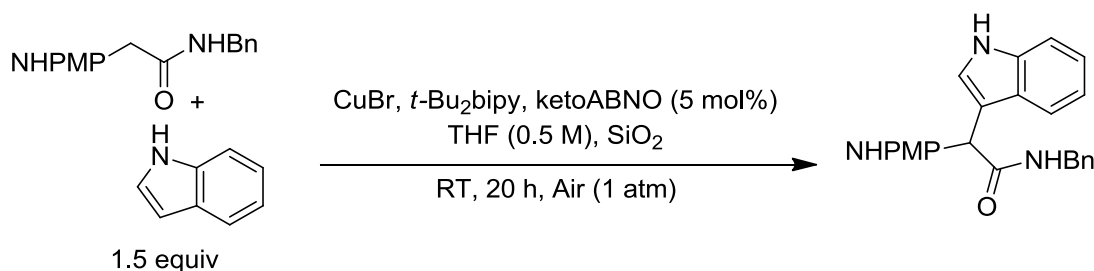


Figure 2.13 Cross dehydrogenative coupling reaction.²⁰

KetoABNO has since been shown by Stahl and co-workers to have application in alcohol oxidation in combination with copper(I) triflate and 4,4'-dimethoxy-2,2'-bipyridine ($^{\text{MeO}}$ bpy).²² However, the initial testing by the group showed ABNO to have a higher reactivity than ketoABNO, and so ABNO was chosen as the optimum radical to use for a substrate scope.

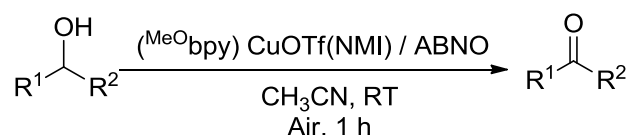


Figure 2.14 Reaction conditions to show aerobic alcohol oxidation using ABNO/ $\text{Cu}(\text{MeCN}_4)\text{OTf} / ^{\text{MeO}}$ bpy system.²²

An extensive substrate scope was carried out under these reaction conditions, showing high yields with benzylic, allylic and aliphatic substrates. The authors commented that no difference in rate is observed between benzylic, allylic and aliphatic alcohols, stating that each were oxidised with nearly equal efficiency. Some limitations of the system were also discussed, which unsurprisingly showed correlation with the limitations observed with the initial copper(I) system.¹⁰ These included substrates bearing terminal alkynes and phenols, the latter having previously been suggested to be due to co-ordination of the – OH group to the copper, thus deactivating the catalyst.

In close succession, Muldoon and co-workers reported a similar system that utilised copper(I) iodide, ketoABNO and bipyridine, also using NMI as a base. They highlighted that due to the high reactivity of the ketoABNO radical, the reactions at catalyst loadings of 1 mol% radical were mass transfer limited, and so only when the catalyst loadings were greatly decreased, was a difference in reactivity observed between activated and aliphatic alcohols. The radical catalyst loading could be dropped to 0.05 mol% and in some cases as low as 0.01 mol% to still display high reactivity. It was also observed that the copper co-catalyst was deactivating as the reaction proceeded.²³ Nevertheless, the reported system is an improvement on the previously

reported copper(I) system, as it exhibits much higher reactivity with aliphatic alcohols, and also solves the problem of secondary alcohol oxidation.

However, as previously mentioned there is still a limitation of this type of aerobic oxidation system consisting of a first row transition metal in combination with a nitroxyl radical co-catalyst, and that is the co-ordination of phenols and anilines to the transition metal, causing catalyst deactivation. The deactivation of the catalyst also means that the catalyst system cannot be recycled. This may not be a problem in the pharmaceutical industry, however if these expensive radicals were to be considered for use in the production of fine chemicals such as fragrance and flavour molecules, the ability to recycle the radical is vital. These problems can potentially be overcome by using non-metal containing systems in combination with NO_x gases. This type of reaction is similar to the previously discussed Anelli's bleach conditions¹⁸ but has the ability to use oxygen or air as the terminal oxidant, and does not require NaOCl which in turn prevents the formation of undesired halogenated side products.

2.1.3 Metal-Free Aerobic Alcohol Oxidation *via in situ* Formation of *N*-Oxoammonium Salts

Metal-free oxidation systems have been of interest in the last ten years, not only with the aim of solving substrate scope limitations of other systems, but the lack of metal is highly advantageous as it prevents the costly purification procedures required to remove metals to the ppm scale necessary in the production of pharmaceuticals.⁷ This style of system utilises TEMPO or other aforementioned nitroxyl radicals, which can be oxidised *in situ* with the aid of a co-oxidant to form the respective *N*-oxoammonium cation capable of oxidising the substrate. The NO_2 formed allows for the regeneration of the oxoammonium salt.

The first example of this type of system was demonstrated by Hu and co-workers in 2004. The system was comprised of TEMPO, bromine, and sodium nitrite in dichloromethane as shown below in Figure 2.15.²⁴

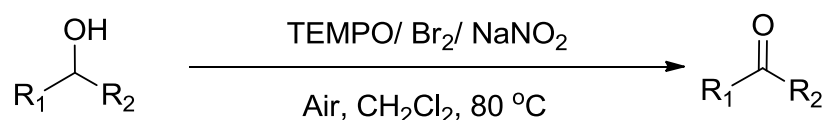


Figure 2.15 Conditions used by Hu and co-workers in the first reported transition metal-free aerobic oxidation system.²⁴

The concept behind the design of this type of system was derived by work previously reported by Bjørsvik *et al*, who demonstrated that a combination of TEMPO and chlorine gas could be used for oxidation, with sodium hydrogencarbonate to neutralise the hydrogen chloride byproduct.²⁵ Hu and co-workers assumed that perhaps by oxidising the hydrogen chloride with oxygen, to regenerate chlorine *in situ*, a catalytic system could perhaps be created. Bromine gas and sodium nitrite were employed as the halogen and NO_x source respectively. Sodium nitrite was chosen based on its redox ability and availability. The optimised reaction conditions allowed for the oxidation of a wide scope of primary and secondary alcohols, also demonstrating a tolerance to a variety of heteroatoms. As with this first example, many other early NO_x systems contained halogenated co-catalysts such as hypochlorous acid (HOCl),²⁶ and sodium bromide in combination with sodium bromate.²⁷ Alternative sources of NO have also been explored, these include *tert*-butyl nitrite (TBN) and iso-amyl nitrite (IAMN).²⁸

Further study of the catalytic system has shown that the reactions can be performed in the absence of halogenated co-catalysts. The first example of this was by Hu and co-workers.²⁹ The suggested catalytic cycle can be seen in Figure 2.16 on the next page.

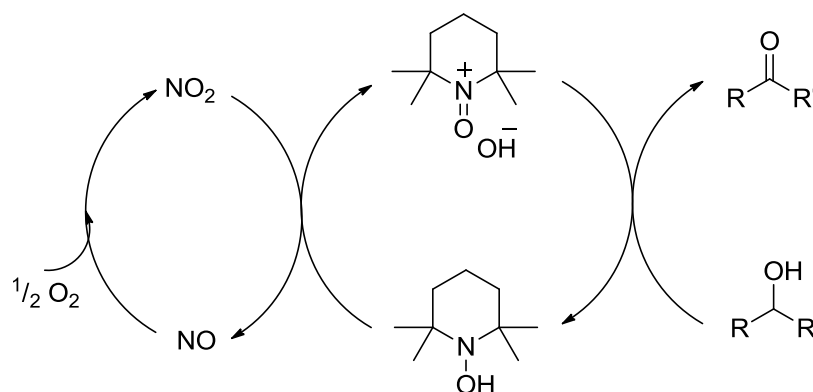


Figure 2.16 Catalytic cycle under halogen- free conditions.³⁰

In this case, the *tert*-butyl nitrite is thermally decomposed to release NO or NO₂. NO₂ oxidises the TEMPO to produce the oxoammonium cation, which can then in turn oxidise the substrate to give the desired carbonyl product. The TEMPO is reduced to form TEMPOH, which can react further with NO₂ to return to the oxoammonium cation. The cycle is completed by the reoxidation of NO by the terminal oxidant, oxygen. In comparison to previously reported systems, a higher loading of NO source is required in order to achieve similar yields. In this case 4 mol% in contrast to the 0.4 mol% required when halide is present. However, the benefits of a halide free reaction system compensate for the necessary increase in NO source.

Recently, TBN has also been used to oxidise alcohols anaerobically. In this case the reaction conditions consist of TEMPO, TBN and a boron ion source in dichloromethane. Holan *et al* utilised the NO⁺ / NO[•] pair to regenerate the oxoammonium cation from TEMPOH.³¹ They compared various boron ion sources, solvents and temperatures, and the optimum conditions found are shown in Figure 2.17.

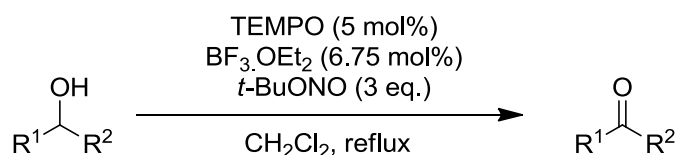


Figure 2.17 Anaerobic transition metal-free alcohol oxidation.³¹

Benzylic and allylic alcohols could be oxidised with ease under these conditions, however aliphatic substrates only gave moderate results. It was found that if a second addition of TEMPO was added further into the reaction, the conversion could be almost doubled. It was also noted that only one equivalent of $\text{BF}_3 \cdot \text{OEt}_2$ should be added. The decreased reactivity with aliphatic substrates was explained by an NMR study that showed that there was a competing reaction involving nitroso group transfer to produce aliphatic nitrites and *tert*-butanol. This showed that only small amounts of free alcohol are free at any given time, explaining the much slower rate of reaction. The authors also demonstrated that it was possible to oxidise menthol under these conditions, if TEMPO were replaced with AZADO. The mild oxidation conditions employed also allowed for the oxidation of enantiopure alcohols that contain labile stereocentres at the α position and so in these cases, no racemisation was observed. This was confirmed by the reduction of the oxidised product to once again yield the enantiopure starting substrate.

Nitric acid has also been suggested as another option, which would be highly advantageous as it is an inexpensive source of NO_x . The first example of this was reported by Kakimoto and co-workers in late 2010. They demonstrated that by using a system consisting of activated carbon, nitric acid and TEMPO, it was possible to oxidise benzylic and aliphatic primary and secondary alcohols with high conversion and almost 100 % selectivity. This system is an improvement on one previously reported by the same group which demonstrated that by using nitroxide radicals in a nitric acid assisted carbon catalysed oxidation system (NACOS) it was possible to efficiently oxidise benzylic alcohols.³² They highlighted that the problem with their current system stemmed from a poor kinetic reactivity to convert the hydroxy group to the carbonyl and suggested that by adding a co-catalyst it may be possible to create a more kinetically favored reaction cycle, resulting in a higher selectivity for the conversion of the alcohol to an aldehyde or ketone. It was determined that nitroxyl radicals would be ideal in such a system as they have been shown to be successful in a wide range of alcohol oxidation systems. A variety of nitroxyl radicals were tested including TEMPO, AZADO and 1-Me-AZADO.

The results showed that the use of radical allowed for an expansion of substrate scope to include aliphatic alcohols. As expected, 1-Me-AZADO and AZADO could obtain the same conversion in less than half the reaction time than that of TEMPO, however, due to the cost of these radicals, TEMPO was chosen as the radical to focus on. It was shown that the rate of reaction was independent of substrate concentration, suggesting that the reaction between the oxoammonium cation and the alcohol is not the rate determining step of the reaction. It was observed that benzyl alcohol could be oxidised without the presence of activated carbon, however the conversion only reached 10% in twenty hours, demonstrating the importance of AC in this system. This also would suggest that the rate determining step is the re-oxidation of TEMPOH to TEMPO. Overall, it was shown that the addition of nitroxide radicals into the NACOS system greatly enhanced the catalytic system as it allowed for reduced solvent, improved reactivity, selectivity and a wider substrate scope.

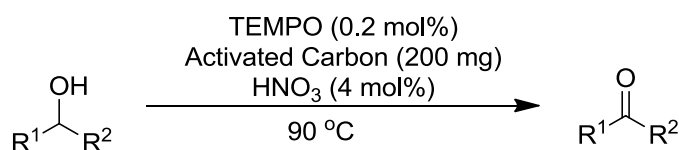


Figure 2.18 Conditions used in NACOS system.³⁰

In 2011, Hermans and co-workers carried out a study on the use of nitric acid for the oxidation of benzyl alcohol under flow conditions.³³ They highlighted that in this type of system, nitric acid is being used as both an acid and an oxidising agent, and that our understanding could be improved by an attempt to separate these two roles. This was done by using solid acid catalysts and sub-stoichiometric amounts of nitric acid. It was found that with standard solid acid catalysts (zeolites), disappointing results were observed. It was hypothesised that the reason for that may be due to strong initial absorption of nitric acid and NO_x species, perhaps inhibiting the reaction. Amberlyst- 15, a protonic ionic exchange resin (insoluble polymer support matrix) gave more promising results. This shows that HNO₂ (formed by the protonation of NO₂⁻) is vital within the reaction. It was demonstrated that the HNO₂ reacts with the

alcohol to produce the nitrite ester, which in turn undergoes acid catalysed decomposition to form the aldehyde product and HNO.

Recently, more studies have been carried out using sterically unhindered radicals in combination with a NO_x source. Iwabuchi and co-workers highlighted that the transition metal-free systems that have been previously mentioned here do have their advantages; halogen-free and metal-free, however they are still limited in terms of substrate scope.³⁴ The majority of the aforementioned systems are only applicable to benzylic alcohols and simple aliphatics. If these systems are ever to be considered as a replacement for the current industrial bleach systems¹⁸ the substrate scope must be broadened. They suggested that in order to do this, TEMPO could be replaced with sterically unhindered radicals, and so be applicable to a wider range of substrates. Using menthol as a model substrate, the reaction was carried out with 5 mol% of various radicals, and 10 mol% sodium nitrite in acetic acid at room temperature. (Figure 2.19)

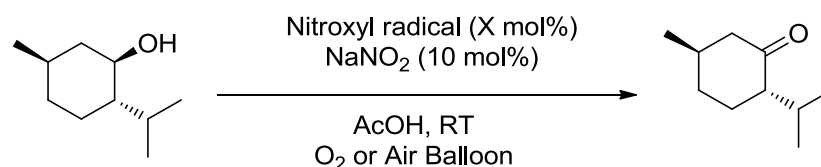


Figure 2.19 Conditions used to determine the catalytic efficiency of various nitroxyl radicals in combination with oxoammonium salts for aerobic alcohol oxidation.³⁴

A large difference in reactivity was observed between TEMPO and the sterically unhindered radicals. TEMPO gave a yield of 5% after 168 hours, in comparison to 1-Me-AZADO and AZADO which gave yields of 71% (24 hours) and 88% (9 hours) respectively. In light of these positive results, the group wished to further improve the catalytic efficiency by placing electron withdrawing groups on the radical. This was done with the assumption that the rate determining step of the reaction is the reaction between the substrate and the oxoammonium cation, in which the presence of an electron withdrawing

group should increase the electrophilicity of the oxoammonium cation, therefore increasing the electrostatic interaction between the substrate and radical species. Several functional groups including –OH, –OMe and –F were added to 1-Me-AZADO and AZADO, with the highest yield being obtained with 5-F-AZADO (92% in two hours). Until this point all reactions had been carried out under pressurised oxygen, however with 5-F-AZADO, a yield of 90 % could be obtained in two hours using an air balloon. If the radical was dropped to a lower catalyst loading of 1 mol%, a 90% yield could still be obtained in an extended reaction time of 9 hours. When TBN was tested as an alternative NO_x source to NaNO_2 , a yellow precipitate remained at the end of the reaction which was found to be $5\text{-F-AZADO}^+\text{NO}_3^-$.³⁴ It was shown that this oxoammonium species was the active species within the reaction; even proving to be an efficient catalyst in its own right, as when added by itself a 96% yield of menthone was obtained within 2 hours, using air as the oxidant. Under either set of conditions shown in Figure 2.20 it was possible to oxidise a wide range of primary and secondary alcohols to their corresponding carbonyl compounds. Even nucleic acid derivatives such as 1,2:4,5-di-O-isopropylidene- β -D-fructopyranose could also be oxidised, a transformation that cannot be performed by the aforementioned bleach conditions. This highlights the extreme potential and importance of such systems, both academically and industrially.

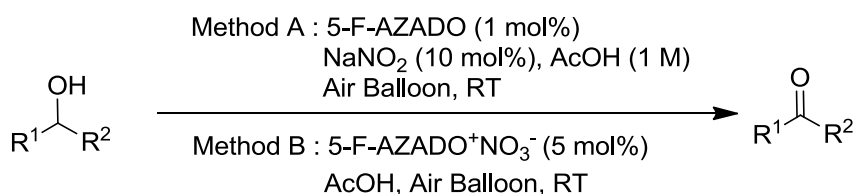


Figure 2.20 Reaction conditions used to examine the scope of aerobic oxidation using F-AZADO and NaNO_2 / $5\text{-F-AZADO}^+\text{NO}_3^-$.³⁴

In late 2013, Lauber and Stahl highlighted that although the 5-F-AZADO used by Iwabuchi and co-workers was highly effective, the expensive multistep synthesis is a major disadvantage and infact similar results could be achieved using ABNO or ketoABNO.³⁵ An additional advantage of this is the increasingly facile synthesis of ABNO or ketoABNO against that of AZADO. It was observed

that there was no correlation between the catalytic activity of the radical and their redox potential. Both acetic acid and acetonitrile were tested as solvents for these reactions, however in the case of acetonitrile; an additional 20 mol% nitric acid was added to the reaction. The reactions also showed a dependence on the terminal oxidant utilised i.e. air or oxygen. In order to compare these different sets of conditions, three separate systems were set up, these can be seen in Figure 2.21.

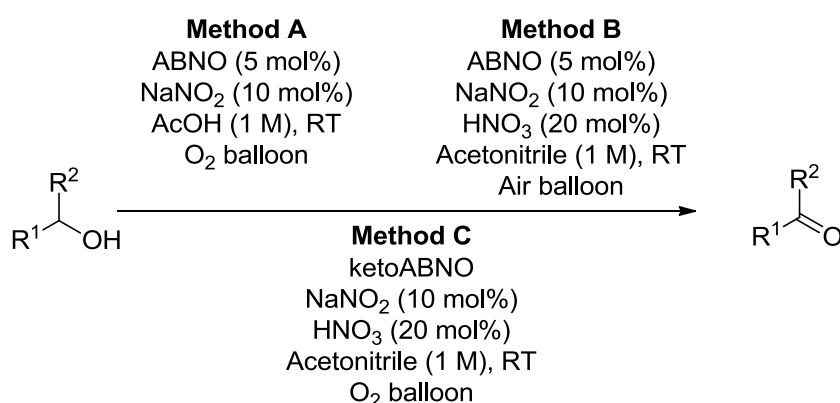


Figure 2.21 Conditions used to demonstrate the scope of ABNO/ ketoABNO catalysed aerobic oxidation of alcohols.³⁵

The results showed that various substrates were suited to either methods A, B or C, however Lauber and Stahl did not probe into what the reason for these preferences may be. Overall, a greater yield was obtained using an oxygen balloon than an air balloon. The ABNO/ acetic acid method showed success with various activated alcohols including a propargylic alcohol, an allylic alcohol, alcohols containing thiophene and pyridine substituents and vicinal *N*-protected amino alcohols. It was also noted that the ketoABNO/ AcOH method was highly efficient with alcohols containing pyridine substituents. Limitations of the substrate scope were also highlighted, with these bearing a similarity with those previously outlined by Hoover and Stahl.¹⁰ Anilines were problematic, and observations under each set of conditions suggest the formation of a diazo compound. Alcohols containing tertiary amine functionalities were also not oxidised successfully, the reason for this was suggested to be an interference with the acid promoted NO_x redox cycle.

Overall, it was shown that by appropriate choice of method, it is possible to use these conditions to aerobically oxidise a vast array of alcohols.

Kanai and co-workers have since demonstrated the application of ketoABNO in combination with NaNO_2 and acetic acid for the oxidation of α -fluoroalkyl alcohols.³⁶ These are generally resistant to mild oxidative conditions due to their obvious electron deficiency, however under these conditions could be oxidised with ease at room temperature under 1 atm oxygen. The system could be applied to a wide variety of aromatic and aliphatic fluorinated substrates to give the desired product in high yields.

2.1.4 Immobilisation of Radicals in Transition Metal-Free Aerobic Oxidations of Alcohols *via in situ* Formation of *N*-Oxoammonium Salts

These systems are a vast improvement on traditional systems in terms of 'green chemistry'; they use oxygen as the terminal oxidant, operate under mild reaction conditions and use less harmful reagents such as sodium nitrite or *tert*-butyl nitrite in contrast to potassium dichromate or manganese oxide. However, the economics of such systems still do not seem feasible. It has been said that even TEMPO is still considered to be expensive in industry with its cost estimated to be 80-100 \$/kg, and in order for it to be economically feasible it would need to be 20 \$/kg.³⁷ Whereas this price range is feasible for the production of pharmaceuticals, 80-100 \$/kg is too expensive when producing perfume or flavour molecules. It is important to note that TEMPO although considered expensive is still vastly cheaper than any of the sterically unhindered class of radicals that have been mentioned here, as currently despite being commercially available, they aren't produced on a large scale. It is probable that in the future this shall change; however due to their more complex synthesis they are likely to remain more expensive than TEMPO. If these methods are going to ever be serious considerations for industrial use then it is necessary to develop ways of recycling the expensive component of the system *i.e.* the radical.

2.1.4.1 Radical Recycling *via* Immobilisation onto Silica

Unsurprisingly, in recent years, attention has been drawn to the development of systems whereby the radical is immobilised, through the use of immobilisation onto silica, anchoring in ionic liquids or even in one case through the use of magnetism.

Karimi *et al.* were the first to demonstrate the use of silica immobilised TEMPO under NO_x style conditions.³⁸ They chose to use SBA-15 as a solid support material due to the size of its pore diameters and high thermal and hydrothermal stability. The silica supported catalyst was prepared using methods reported previously in the literature³⁹ by carrying out a reductive amination with aminopropyl functionalized SBA-15 and 4-oxo-2,2,6,6-tetramethylpiperidine. The finished solid supported catalyst can be seen in Figure 2.22. Using benzyl alcohol as a model substrate, the reaction was carried out with 1 mol% of SBA-15 supported TEMPO, 10 mol% NaNO_2 , 8 mol% $[\text{NBu}_4][\text{Br}]$, in acetic acid, for an hour and a half at 50 °C under a 1 atm pressure of oxygen.

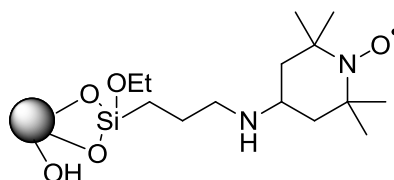


Figure 2.22 SBA- 15 supported TEMPO.³⁸

It was shown that this catalyst system could successfully oxidise primary and secondary alcohols with ease, even oxidising sterically hindered alcohols such as isoborneol with a 100% yield in ten hours. The system was shown to be applicable to a wide range of alcohols, including those with nitrogen and sulphur heteroatoms. The reactions could also be carried out under air as an alternative to pure oxygen, however in these cases, an extended reaction time was required.

To investigate the recyclability of the catalyst, benzyl alcohol was used with a reaction time of 1.5 hours. The catalyst was filtered from the reaction mixture,

with the aldehyde conversion at 60%. The filtrate was left to 'react' for a further five hours, in which time no additional conversion occurred, demonstrating that all the catalyst is removed by filtration, and no leaching of the radical is observed. The solid catalyst was used for fourteen runs, and then several forms of analysis were carried out and compared with the data obtained prior to the first run. The methods of analysis used included TEM (transmission electron microscopy), and DRIFT (diffuse reflectance infrared fourier transform). All methods indicated the catalyst to have a high durability under the reaction conditions.

Di and Hua also demonstrated the immobilisation of TEMPO onto silica, however this time using porous silica beads, with the additional advantage of storing NO_x gas within the solid catalyst support.⁴⁰ Benzyl alcohol was once again chosen as the model substrate and tested initially with 0.3 g, 0.5 g and 0.7 g of catalyst. The reactions took 15 hours, 4 hours and 2.5 hours respectively to achieve a conversion of 99% with 99% selectivity. From this it was determined that 0.5 g would be the appropriate catalyst loading. The reaction was carried out in an open flask, at room temperature. The cycle was repeated ten times, with little variance in reactivity, with surface area, pore volume and pore diameter remaining almost constant indicating that the catalyst is suitable for recycling.

In 2011, Karimi *et al* also demonstrated the use of aminoxyl radicals immobilised onto silica coated Fe_3O_4 nanoparticles.⁴¹ A 0.2 mol% catalyst loading was used in combination with 4 mol% TBN, in 0.3 mL of water at 50 °C to oxidize primary and secondary benzylic and allylic alcohols. Moreover, the oxidation of sterically bulky substrates such as menthol, 2-adamantol and isoborneol could be oxidised in high yields of 90%, 94 % and 82% respectively, with extended reaction times. After the completion of the reaction the catalyst was separated from the reaction mixture by the use of an external magnet and then washed with ethanol and water. The catalyst was successfully re-used twenty times without loss in catalytic activity.

In 2014, the same group demonstrated the use of silica supported ABNO in a system comprised of TBN, and acetic acid in toluene.⁴² (Figure 2.23) The system was run at 50 °C under pure oxygen (1 bar), and could successfully oxidise primary and secondary benzylic and aliphatic alcohols. The system could oxidise more sterically demanding alcohols such as menthol, isoborneol and adamantol; however if the silica-ABNO was replaced with previously used silica-TEMPO, poor yields of 12%, 18% and 15% were achieved respectively. Using benzyl alcohol as a model substrate, it was demonstrated that the immobilised catalyst could be used consecutively for up to 12 runs without dramatic loss in activity. BET (Brauner Emmett Teller analysis) and TGA (thermal gas analysis) showed little change in the catalyst structure after several runs. They highlight that the high stability of the catalyst is thought to be due to the strong covalent bonding of the ABNO inside the pores of the SBA-15, which results in a decreased loss of organic catalyst into the solvent phase.

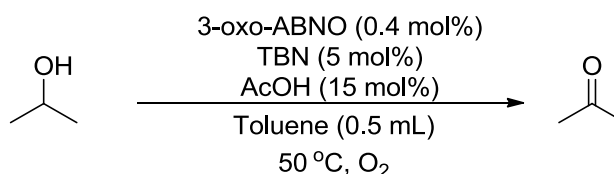


Figure 2.23 SBA-15 functionalised ABNO system.⁴²

Probably the most effective way to use silica supported catalysts is under a continuous flow system such as that recently demonstrated by Aellig *et al.*⁴³ They highlighted that current NO_x systems could be improved by utilising a continuous flow system as this would increase the catalyst to substrate ratio and in turn also improve the mass transfer. An additional advantage is that the amount of co-oxidant required (such as TEMPO) can be decreased. A liquid feed of substrate, nitric acid, solvent and biphenyl was combined with oxygen and pumped through a packed bed reactor containing commercially available silica supported TEMPO. The catalyst was shown to deactivate at temperatures above 55 °C due to acid catalysed decomposition. The presence of N₂O was confirmed by gas phase IR (infrared spectroscopy). EPR (electron

paramagnetic resonance) of the catalyst prior to and after the reaction also proved significant loss of TEMPO during the reaction. The catalyst was shown to be stable below 55 °C. A select substrate scope was carried out, demonstrating that alcohols such as prenol which usually suffer from dehydration under acidic conditions could successfully be oxidised. Renewable substrates including lactic acid and 5-hydroxymethylfurfural were also efficiently oxidised.

2.1.4.2 Radical Recycling *via* Ionic Liquids

Another possible method that has been suggested for the recycling of radicals is to design an ionic liquid containing the nitroxyl radical, thus have the multipurpose of catalysing the reaction and allowing for catalyst recycling. One of the early examples of this was a three component catalyst system proposed by Miao *et al.* which consisted of a TEMPO functionalised imidazolium salt ([Imim-TEMPO]⁺X⁻), a carboxylic acid substituted imidazolium based ionic liquid ([Imim-COOH]⁺X⁻) as a source of acidity which is generally required in these reactions, and NaNO₂ as the source of NO_x, as shown in Figure 2.24 below.⁴⁴

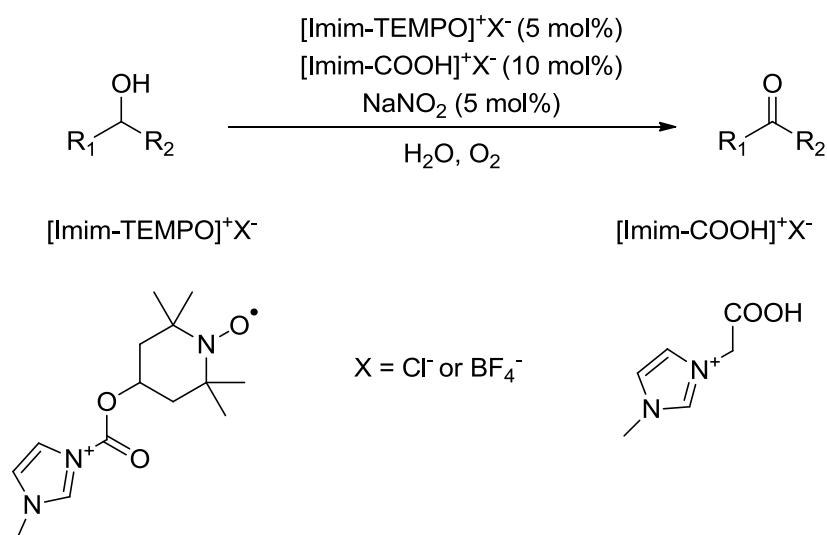


Figure 2.24 Aerobic oxidation of alcohol catalysed by [Imim-TEMPO]⁺X⁻/ [Imim-COOH]⁺X⁻/ NaNO₂.⁴⁴

The catalyst system was initially tested with benzyl alcohol to give very promising results. Preliminary testing showed that the addition of water up to 0.2 mL dramatically increased the yield by increasing the catalyst solubility. Primary benzylic alcohols were oxidised in less than an hour to give yields ranging from 80 – 100%. Secondary benzylic alcohols were also oxidised, although as expected these required an extended reaction time. Aliphatic alcohols such as dodecanol could be oxidised however the system struggled to oxidise 2-octanol and 1-heptanol. The catalyst could be used up to four runs with only a slight decrease in catalytic activity at the end of the fourth run. The catalyst was recycled by separating the water phase of the reaction, adding new substrate and replenishing the NaNO_2 .

In 2011, the same group published another paper utilising a task specific ionic liquid synthesised from commercially available 4-hydroxy-TEMPO, chloroacetic acid, 1-methylimidazole and iron(III) chloride.⁴⁵ The IL was shown to have paramagnetic properties, proven through the use of SQUID (superconducting quantum interference device) measurements. The ionic liquid can be seen in Figure 2.25.

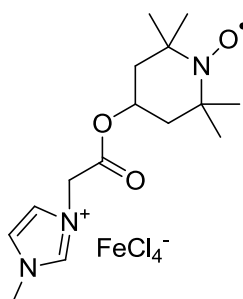


Figure 2.25 Fe/ TEMPO based magnetic ionic liquid [Imim-TEMPO][FeCl₄].⁴⁵

Testing initially was carried out using benzyl alcohol as the model substrate with 5 mol% of the bimagnetic ionic liquid. The reaction conditions were optimised, to give a 100% conversion to benzaldehyde in 1.5 hours at 30 °C, and O₂ (2 bar). As before, it was shown that the catalytic efficiency of the reaction could be improved by the addition of water. Primary and secondary benzylic alcohols could be oxidised with ease to their corresponding carbonyl

A polyethylene glycol ionic liquid was also demonstrated to be a viable option for the aerobic oxidation of alcohols by Zhu *et al.*⁴⁶ The temperature dependent ionic liquid [Imim-PEG600-TEMPO][OMS] (Figure 2.26) was used in a mixed solvent of cyclohexane and carbon tetrachloride (4:6). At 60 °C this mixed solvent allowed for the IL to be miscible within the solvent, however when cooled became immiscible allowing for facile catalyst separation. The catalyst system was similar to those previously discussed, consisting of 1 mL IL, 10 mL of mixed solvent, 5 mol% NaNO₂ and 10 mol% sulfuric acid.

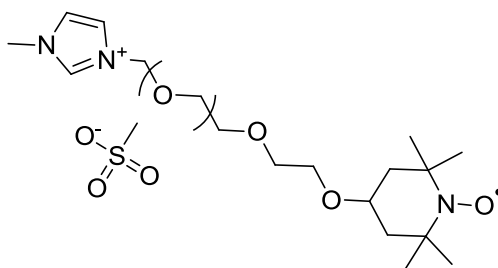


Figure 2.26 Temperature dependent ionic liquid [Imim-PEG600-TEMPO][OMS].⁴⁶

These conditions were tested for a variety of benzylic primary alcohols to give high conversions within 2-6 hours. Aliphatic alcohols proved problematic under these reaction conditions, even when extended reaction times were applied. The reaction mechanism was suggested to be similar to those previously reported in the literature for NO_x systems. The catalyst was recycled at the end of the reaction by cooling the reaction to room temperature, decanting the organic phase and then the ionic liquid phase could be recycled without any further purification. The catalyst showed little loss in catalytic activity after five runs.

As can be seen, there are several advantages to using ionic liquids; they allow for catalyst recycling, in some cases may have positive effects on the activity

of the reaction, and their negligible vapour pressure is favourable when considering safety as an alternative to traditional, flammable organic solvents. However, ionic liquids also have drawbacks associated with them. Firstly, ionic liquids are costly, and when used as a solvent, large quantities are required. Problems also can arise in terms of mass transfer limitation due to the increased viscosity of ionic liquids. Through the use of supported ionic liquid phase catalysts, (SILPS) it is possible to negate these drawbacks.

2.1.4.3 Radical Recycling *via* SILPS

A SILP consists of three main components, a catalyst, which is dissolved in an ionic liquid, which is then in turn immobilised onto a support material, such as silica, to form a free flowing, heterogeneous catalyst.⁴⁷ In this case, the reaction occurs within the ionic liquid layer, as with homogeneous reactions in ionic liquids, therefore allowing for high levels of activity and selectivity. The immobilisation allows for the enhancing of catalyst stability and enables the potential for recycling. In addition, by immobilising the ionic liquid onto a solid support, the quantity of ionic liquid required is in turn reduced, therefore lowering the costs associated with the use of ionic liquids. By applying only a thin layer of ionic liquid to the support, mass transfer limitations are also reduced.

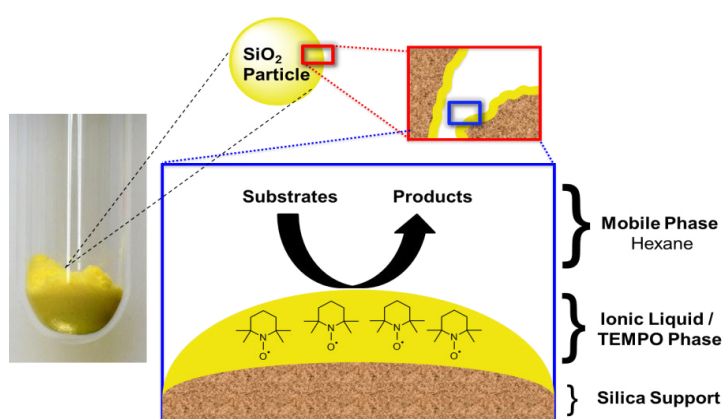


Figure 2.27 Representation of SILP structure.

SILPS have been used in several applications, however some of the earliest examples were shown by Mehnert in 2002, and Wasserschied in 2003 for hydrogenation and hydroformylation reactions respectively. Mehnert and co-workers demonstrated the first use of an ionic liquid phase that contained a homogeneous hydrogenation catalyst, immobilised onto silica.⁴⁸ They reported that the catalyst showed an increase in activity over both the homogeneous IL and biphasic IL reaction systems. It was believed in this case, that the enhancing ionic liquid effect was due to the lack of coordinating solvent, making the metal centres of the catalyst more accessible. The use of a SILP was also shown to decrease limitations caused by mass transfer, as the high surface area silica support, in combination with small amounts of ionic liquid result in an increased concentration of the active rhodium catalyst at the interface (organic solvent: ionic liquid) in comparison to that of the biphasic system, thus resulting in an increase in reactivity. The immobilised catalyst also demonstrated high long- term stability, as it could be used for up to 18 runs without any significant loss in activity.

Wasserscheid and co-workers demonstrated that SILPS could be utilised for rhodium catalysed hydroformylation, following on from previous work that had shown ionic liquids to be useful alternatives to aqueous media in biphasic systems.⁴⁹ The SILP was composed of 1-butyl-3-methylimidazolium hexafluorophosphate and rhodium with a cationic phosphine ligand. It was shown that it could be used for the successful continuous flow, gas phase hydroformylation of propene and 1-octene. Liquid phase hydroformylation with SILPS was also demonstrated for the first time with 1-octene however there was poor solubility of the CO/H₂ gas in the ionic liquid causing gas mass transfer limitations. Benefits were however observed with the SILP catalyst over the biphasic ionic liquid system as very small quantities of ionic liquid were required and there was only a very short diffusion distance due to the thinly dispersed ionic liquid/ catalyst layer, in contrast to the biphasic IL/ organic system.

In 2010, Chrobok and co-workers applied a SILP system to the aerobic oxidation of primary alcohols.⁵⁰ Inspired by the fact that the oxidation of

alcohols using a copper/TEMPO system had already been carried out successfully in ionic liquid,⁵¹ they utilised a SILP in order to allow for a more simplistic catalyst separation and the potential to use a fixed bed reactor. They synthesised two different types of support, choosing to support the copper salt in an ionogel and on bimodal pore structure silica. After each reaction, the catalysts were recycled by washing with diethyl ether and dried under vacuum at 60 °C for five hours. For each re-run the reactions were charged with fresh substrate, TEMPO, and ether. The ionogel catalyst $\text{CuCl}_2/[\text{bmim}][\text{CO}_2\text{SO}_3]$ was shown to be active, however taking a reaction time of 7 hours to oxidise benzyl alcohol to 99% conversion, using a catalyst loading of 5 mol% of both TEMPO and copper(II) chloride. In order to achieve the same conversion, using the silica supported SILP, it was necessary to increase the TEMPO catalyst loading to 10 mol%. Both catalysts could be recycled up to seven times with little loss in reactivity. Whereas this system demonstrates the possible application of SILP systems to the aerobic oxidation of alcohols, the choice to recycle the copper salt within the system instead of TEMPO, seems unusual as the cost of TEMPO outweighs the copper salt. It would therefore seem that if this method of recycling were to be applied, it should perhaps be the TEMPO that is immobilised.

2.1.4.4 Radical Recycling *via* Phase Separation

Kakimoto and co-workers recently demonstrated solvent free aerobic oxidation using 1-Me-AZADO, through the use of the varying solubility of 1-Me-AZADO depending on its oxidation state.⁵² The group highlighted that throughout the reaction mechanism, the solubility of the catalyst varies. Initially it is only partially soluble in water, then once oxidised to the oxoammonium cation it becomes soluble in water and insoluble in the organic phase, then once reduced to the hydroxylamine the solubility is again reversed, once again becoming insoluble in the water phase. Initially three nitroxyl radicals were screened; TEMPO, 1-Me-AZADO and ABNO, as in this case the choice of radical is vital to the success of the catalytic system. Not only must the catalytic efficiency be considered but also the radical stability, as this is a determining

factor in the catalyst recycling step. Through the use of UV-Vis (ultraviolet-visible) spectroscopy it was shown that TEMPO⁺ and 1-Me-AZADO were stable, however ABNO⁺ underwent rapid decomposition. From this 1-Me-AZADO was chosen as the ideal radical as its catalytic activity has previously been shown to be superior to that of TEMPO. The reaction conditions can be seen in Figure 2.28.

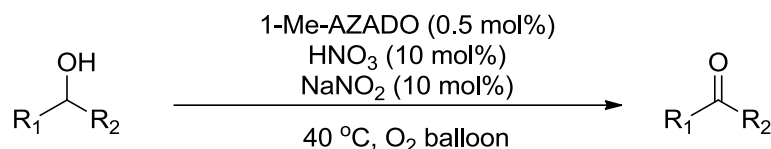


Figure 2.28 Conditions used for the solvent free aerobic oxidation of alcohol with 1-Me-AZADO *via* phase separation.⁵²

Benzyl alcohol was used as the model substrate to demonstrate catalyst recycling. Benzyl alcohol and 1-Me-AZADO were added to a test tube followed by the addition of HNO₃ solution, to which sodium nitrite was added and an oxygen atmosphere applied. The product stays in the organic phase, and the oxoammonium cation goes into the aqueous phase at which point the organic phase is removed to isolate the product and nitric acid solution is added to the aqueous phase to regenerate the catalyst to its initial state. Fresh substrate is added and the reaction can then be repeated. The catalyst was tested up to eight times with only slight catalytic activity being lost in the final run, probably due to both loss of catalyst during the recycling process and consumption of catalyst by oxidative decomposition during the reaction. The system was shown to successfully oxidise benzylic alcohols to 99% conversion in 3-6 hours. 2-Octanol was also tested; however results were disappointing with a conversion of 38% after a reaction time of eight hours. This example demonstrates the vast potential of these systems not only to accommodate aerobic alcohol oxidation in quantitative yields but also to allow the effective recycling of expensive nitroxyl radicals.

2.2 Aims and Objectives

It can be seen from the literature discussed, that the potential for metal-free systems in aerobic alcohol oxidation, is vast. However, there are still some major limitations to be overcome if these systems are to be applied on a larger scale. The first aim of the project was to develop a metal-free catalyst system for the aerobic oxidation of alcohols that utilises nitric acid as a cheap, practical sole source of NO_x . We hoped that when optimising this system to focus on the oxidation of secondary alcohols, as many applicable methods for the oxidation of primary alcohols are already present within the literature. Secondly, we wished to develop a method that could enable catalyst recycling, as currently, the cost of these nitroxyl radicals, especially the more reactive sterically unhindered variant, is a major roadblock when considering their larger scale application.

2.3 Results and Discussion

The first aim of the project was to develop a catalyst system that utilised nitric acid as a cheap, practical source of NO_x . In order to optimise the quantity of nitric acid required, 5 mol%, 10 mol% and 20 mol% nitric acid were combined with 5 mol% TEMPO and tested for the oxidation of 2-octanol. 2-Octanol was chosen as a model substrate for the optimisation of the system as it is a secondary, unactivated alcohol and so is representative of a regularly occurring 'problem substrate' within the literature. The results can be seen in Figure 2.29.

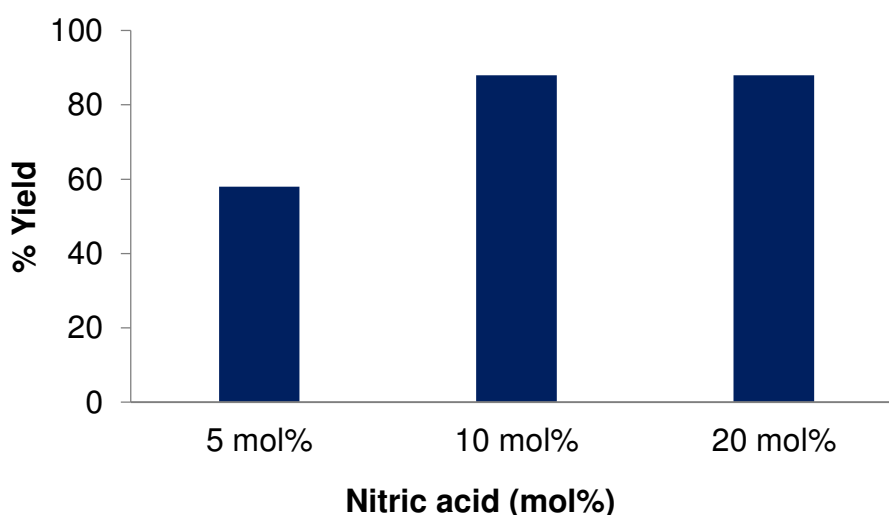


Figure 2.29 Results obtained with varying concentrations of nitric acid.

Reaction conditions; 2-octanol (1 mmol), TEMPO (5 mol%), nitric acid (X mol%), 5 mL acetonitrile, 60 °C, 4 h, 40 bar air, 500 rpm.

As can be seen from the graph, 10 mol% nitric acid was observed to give the optimum yield of 2-octanone. These results are in correlation with a study released by Hermans and co-workers demonstrating that despite the reaction being initially first order in terms of nitric acid, there comes a point when the concentration of nitric acid no longer effects the rate of the reaction, and in fact, too high a concentration results in byproduct formation.³³ For this reason, 10 mol% nitric acid was chosen for the remainder of the study.

Reaction temperature was then examined, testing a range of temperatures between 25 °C and 100 °C with the best result being obtained at a temperature of 60 °C, as can be seen in Figure 2.30.

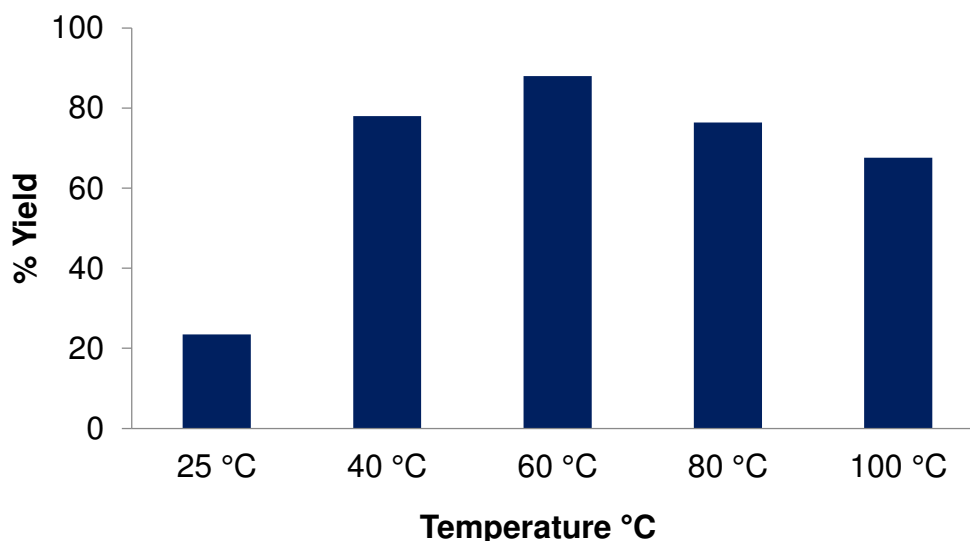


Figure 2.30 Results obtained with varying reaction temperature.

Reaction conditions; 2-octanol (1 mmol), TEMPO (5 mol%), nitric acid (10 mol%), 5 mL acetonitrile, X °C, 4 h, 40 bar air, 500 rpm.

Whereas it may seem self-explanatory that an elevated reaction temperature of 60 °C resulted in an increase in yield, due to the general rule that an increase in reaction temperature results in an increase of rate of reaction; it should be remembered that other oxoammonium cation reactions such as Anelli's bleach conditions, operate efficiently at 0 °C.¹⁸ In this case, we believe that the increase in yield obtained at 60 °C is due to an increase in the breakdown of nitric acid, which is the initiating step in the reaction. It was also observed that too high a reaction temperature was detrimental to the yield obtained, and this is thought to be due to the instability of the oxoammonium cation at higher temperatures.^{30,33}

After the system was optimised in terms of nitric acid loading and temperature, a substrate scope was run testing both TEMPO and ABNO for the oxidation of various alcohols. The alcohols chosen were 2-octanol as used previously, 1-phenylethanol as an example of an activated secondary alcohol, menthol, not only for its steric bulk but also as its ketone derivative menthone is a highly

desirable molecule in the fine chemical industry, and isoborneol, as this is commonly used in the literature as an example of a sterically hindered alcohol.

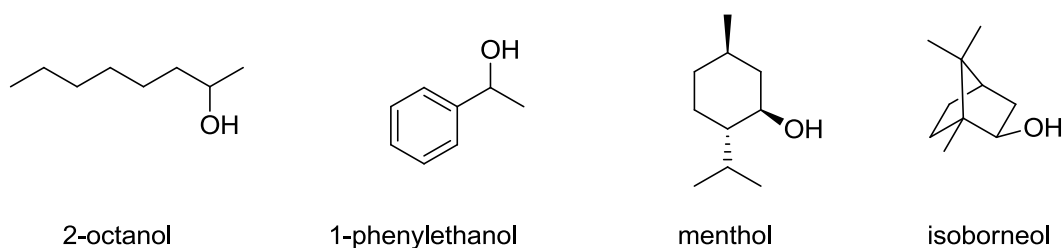


Figure 2.31 Alcohols selected for substrate screen.

For the substrate screen all experiments were run in acetonitrile. This was chosen as a suitable solvent for these reactions as previous studies by the Stahl group showed that acetonitrile could be used as a preferable solvent replacement to dichloromethane, the traditional solvent for NO_x based reactions.³⁵ It was thought that once the system was optimised the reactions would be run in an ionic liquid as a potential method for catalyst recycling. For this reason, all reactions were performed under an initial pressure of 40 bar of compressed air, as it was assumed that once in the ionic liquid, a higher partial pressure would be required due to low oxygen solubility in the ionic liquid. The reactions were also run in a more concentrated volume of 1 mL acetonitrile. The results from the substrate scope can be seen in Figure 2.32.

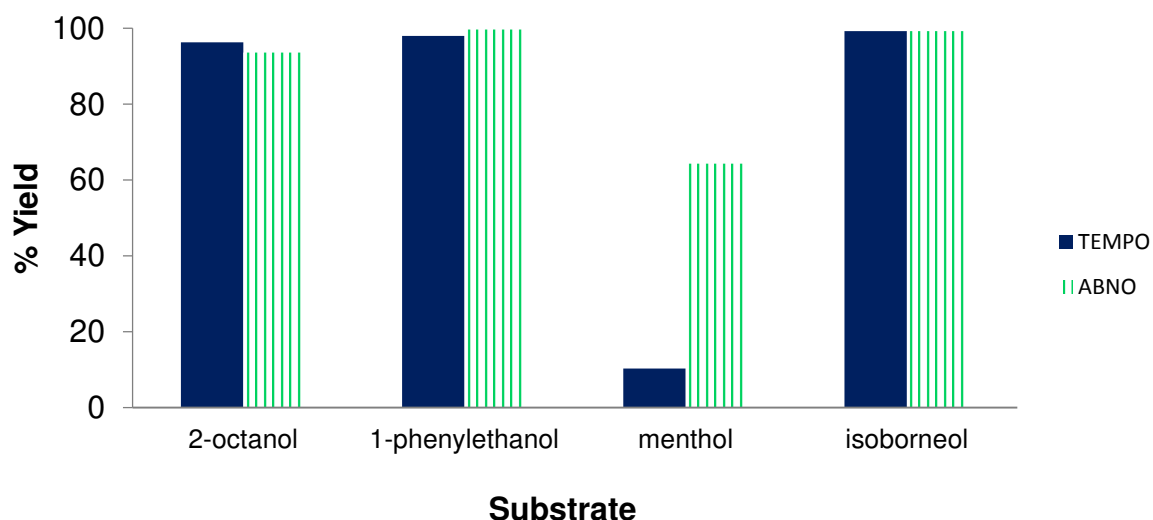


Figure 2.32 Results of substrate scope.

Reaction conditions: Substrate (1 mmol), TEMPO/ ABNO (5 mol%), nitric acid (10 mol%), 1 mL acetonitrile, 60 °C, 4 h, 40 bar air, 500 rpm.

As can be seen from the graph, similar conversions were obtained with both TEMPO and ABNO for all alcohols with the exception of menthol. This is not surprising, as it has been shown in the literature that menthol is particularly slow to react due to its steric bulk. In most cases it is necessary to increase the reaction time or use sterically unhindered nitroxyl radicals.³⁵

The substrate scope was run initially at a pressure of 40 bar air, however it would be preferable if the reaction could be run at a lower gas pressure to alleviate safety concerns in relation to high pressures of oxygen in combination with organic solvents. A gas composition of 8% O₂/N₂ was also tested, as this is in accordance with limiting oxygen concentrations. This is the concentration of oxygen below which combustion of the organic compound in question is not possible, which for most organic compounds lies between 8-12 % O₂.⁵³ Using 2-octanol as the model substrate, the reaction was run using 10 and 40 bar of both gas mixtures, sampling the reaction periodically over a two hour time period. The graph in Figure 2.33 shows the difference observed when comparing 40 bar and 10 bar of air. The rate of reaction with 40 bar of air is initially faster, with the yield obtained levelling off after one hour, to give the same final yield after two hours.

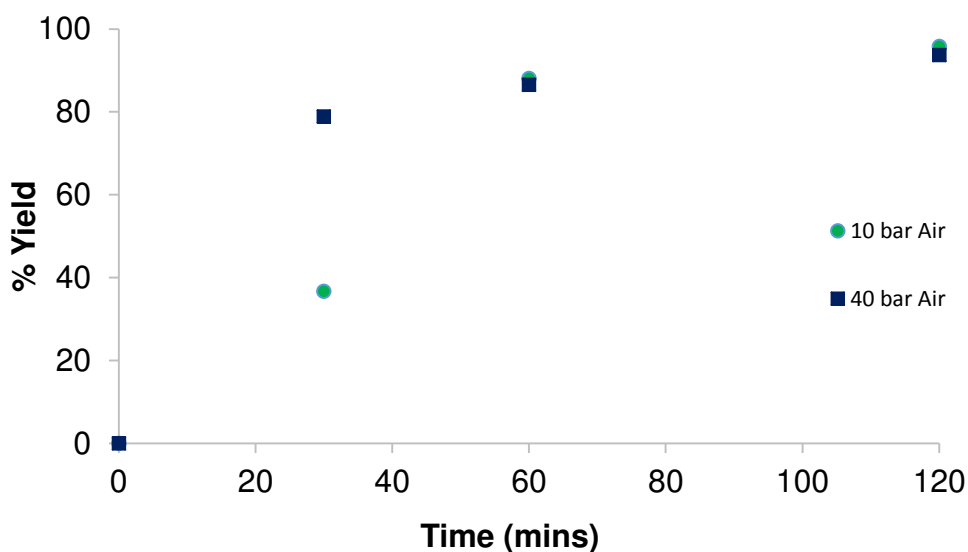


Figure 2.33 Reactivity of 2-octanol under varying air pressure.

Reaction Conditions; 2-octanol (1 mmol), TEMPO (5 mol%), nitric acid (10 mol%), acetonitrile (1 mL), X bar air, 60 °C, 2 h, 500 rpm.

Similar results were obtained when comparing 40 bar of 8 % O₂/N₂ against 10 bar 8% O₂/N₂, as can be seen in Figure 2.34. It was also noted as an overall trend, that those reactions in air were faster than the equivalent pressure in 8% O₂/N₂.

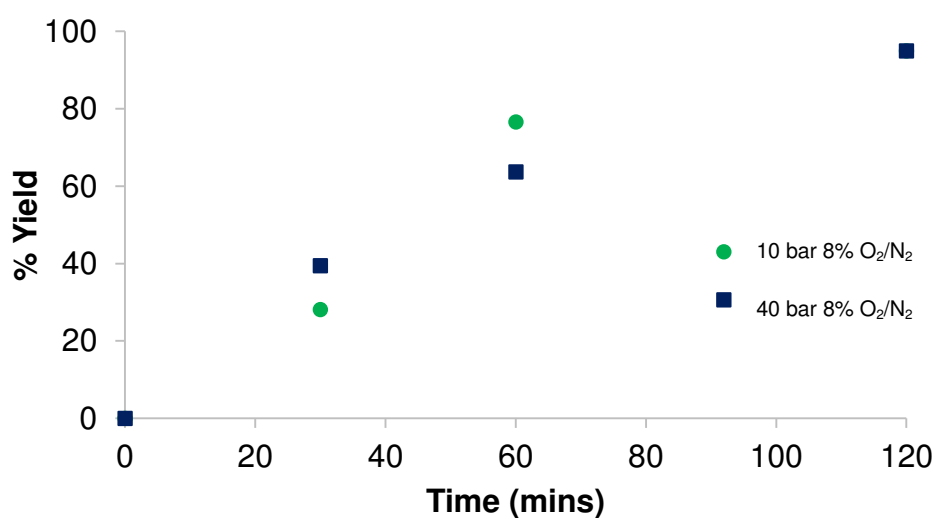


Figure 2.34 Reactivity of 2-octanol under varying pressure of 8 % O₂/N₂.

Reaction Conditions; 2-octanol (1 mmol), TEMPO (5 mol%), nitric acid (10 mol%), acetonitrile (1 mL), X bar 8 % O₂/N₂, 60 °C, 2 h, 500 rpm.

As a further investigation, the same substrate scope as previous was carried out comparing both 40 bar air and 40 bar 8% O₂/N₂, with a reaction time of one hour. If the rate limiting step of the reaction is the reoxidation of NO, then the biggest difference in reactivity with varying gas pressure should be observed with the most reactive substrate, which in this case is 1-phenylethanol. However, as can be seen in Figure 2.35, the opposite trend was observed; with the greatest difference being seen with the least reactive substrate, isoborneol.

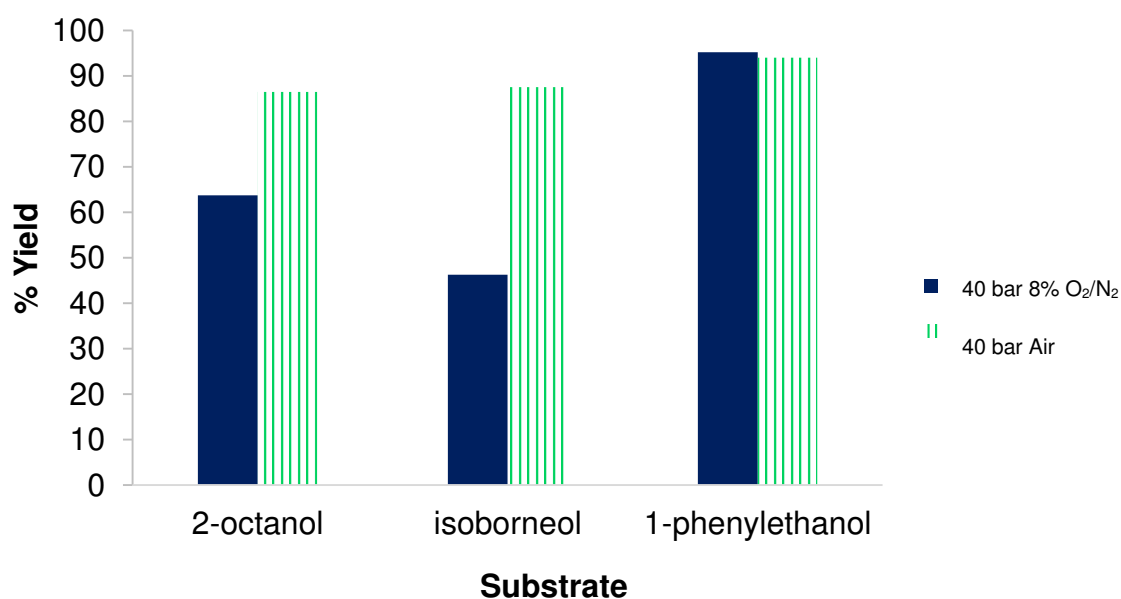
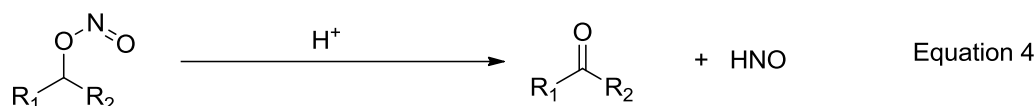
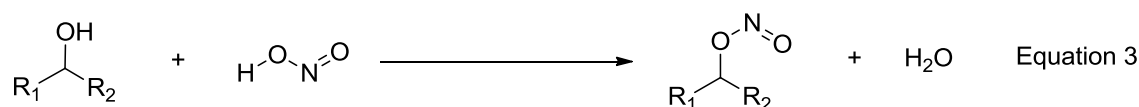
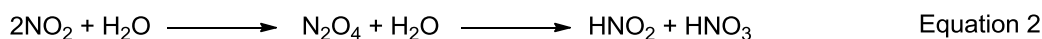
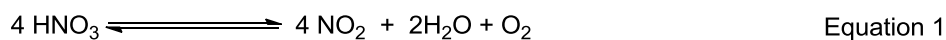


Figure 2.35 Effect of pressure on varying substrates.

Reaction Conditions; substrate (1 mmol), TEMPO (5 mol%), nitric acid (10 mol%), acetonitrile (1 mL), 40 bar gas, 60 °C, 1 h, 500 rpm.

This demonstrates that the reaction is not mass transfer limited in oxygen, but that the oxygen pressure must have some other influence on the reaction. This is in correlation with a report by Hermans and co-workers which shows that the initiating step in the reaction is the breakdown of nitric acid to produce nitrogen dioxide, oxygen and water, as seen in equation one.³³



The reversible nature of this reaction means that at higher oxygen pressures, the equilibrium shifts to favour the production of nitric acid. Another report by Jahn and Holan demonstrated that in a system comprised of TEMPO, *tert*-butyl nitrite and boron trifluoride diethyl etherate, a competing reaction occurs with slower aliphatic substrates whereby the alcohol reacts with nitrous acid to produce the nitrite.³¹ The nitrite can then be broken down *via* acid catalysed decomposition to produce the desired carbonyl compound.³³ It is believed that this may be happening here also, whereby less reactive aliphatic alcohols produce the nitrite, and then require additional acid to allow for the decomposition to occur. Therefore, a higher oxygen concentration is beneficial, as it encourages the formation of nitric acid. It was thought that it may be possible to add an acidic additive to the reaction in order to allow the reactions to be run at lower pressures or a lower concentration of oxygen but achieve the same conversions as those at 40 bar air.

As previously the greatest difference between gas compositions had been observed with isoborneol, it was taken as the model substrate to test several acidic additives, including *p*-toluenesulfonic acid, triflic acid, trifluoroacetic acid (TFA) and an acidic ionic liquid (1, (3-sulfopropyl)-3-methylimidazolium triflate) was also synthesised and tested. For comparison, 20 mol% nitric acid was also tested again, as although this was tested in the initial optimisation, the reaction was optimised with 40 bar air, and so the potential additional benefit may not have been observed. The results can be seen in Figure 2.36.

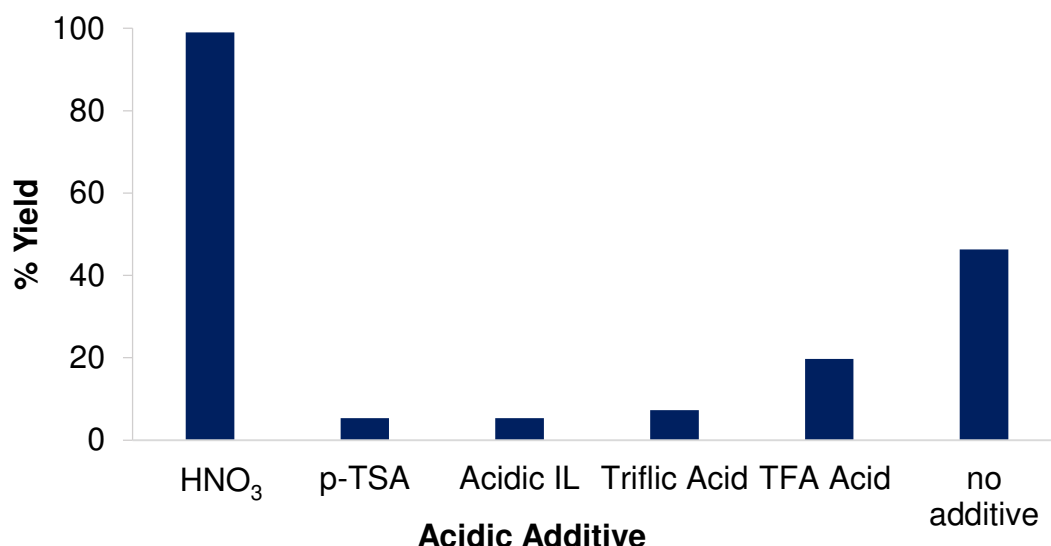


Figure 2.36 Testing of acidic additives with isoborneol.

Reaction conditions; isoborneol (1 mmol), TEMPO (5 mol%), nitric acid (10 mol%), acidic additive (10 mol%) acetonitrile (1 mL), 40 bar 8% O₂/N₂, 60 °C, 1 h, 500 rpm.

From previous results it is known that isoborneol achieves an 88% conversion in 1 hour, when using a pressure of 40 bar air. From these results it was observed that the reaction rate drops vastly with all acidic additives with the exception of additional nitric acid. It was also observed that an additional product was obtained which was found to be camphene, confirmed by GC and ¹H-NMR analysis. This potentially arises from a side reaction of isoborneol, known to be acid catalysed. The side reaction proceeds *via* a Wagner-Meerwein rearrangement to form the undesired camphene product.⁵⁴ As a result of this, isoborneol is not an ideal model substrate to test, and so the same reaction was repeated using 2-octanol as a model substrate. The results can be seen in Figure 2.37.

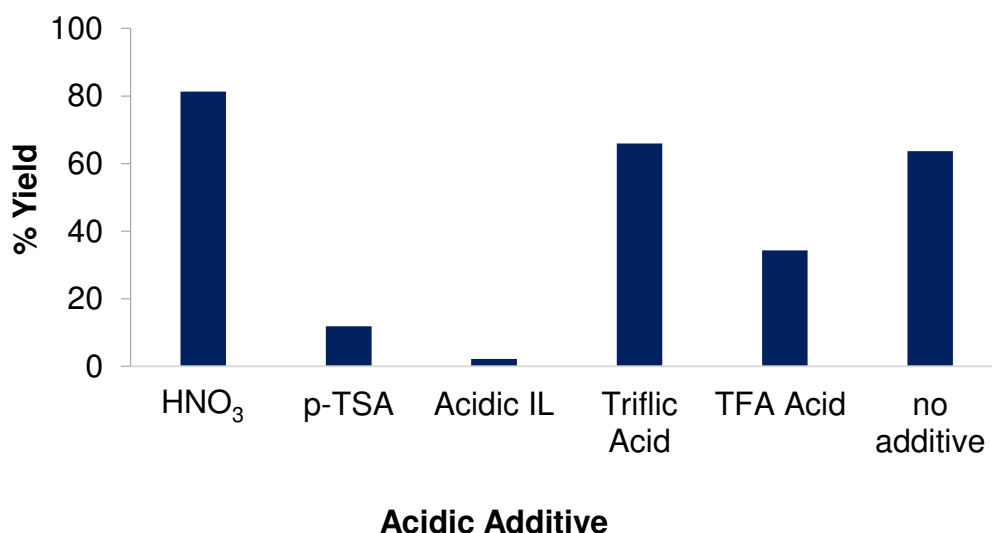


Figure 2.37 Acidic additives tested with 2-octanol.

Reaction conditions; 2-octanol (1 mmol), TEMPO (5 mol%), nitric acid (10 mol%), acidic additive (10 mol%) acetonitrile (1 mL), 40 bar 8% O₂/N₂, 60 °C, 1 h, 500 rpm.

In the case of 2-octanol, a conversion of 87% can be achieved under 40 bar air. It was observed that a similar result of 81% can be achieved if 20 mol% nitric acid is added, when using 40 bar of 8% O₂/N₂. After this initial positive result, it was anticipated that it may be possible to lower the oxygen concentration further, and so several quantities of nitric acid were tested, using a reduced pressure of 10 bar air (equivalent to 2.1 bar O₂). The results can be seen in Figure 2.38.

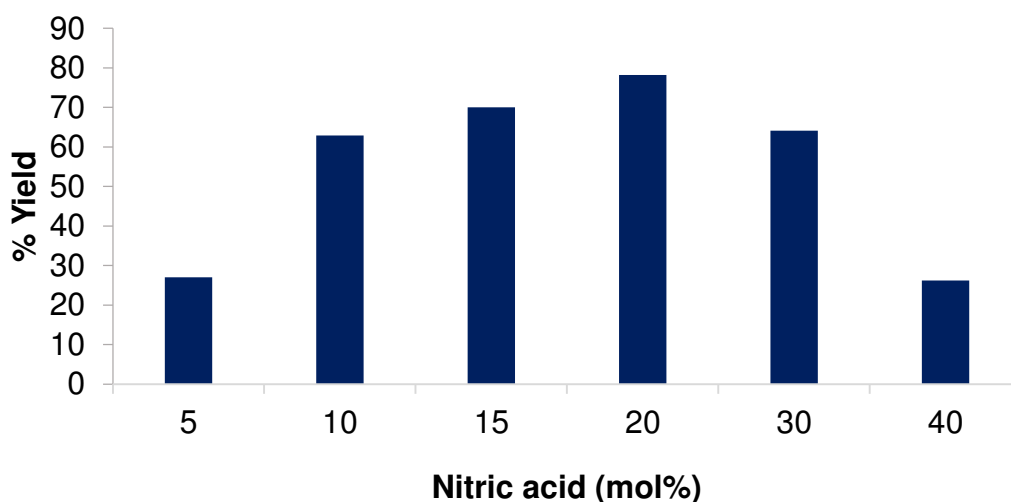


Figure 2.38 Testing different concentrations of nitric acid.

Reaction conditions; 2-octanol (1 mmol), TEMPO (5 mol%), nitric acid (X mol%), acetonitrile (1 mL), 10 bar air, 60 °C, 1 h, 500 rpm.

The results in Figure 2.38 demonstrate that 20 mol% nitric acid allows for a yield of 78%, when using a reduced pressure of 10 bar air. It should be noted that too high a concentration of nitric acid results in a reduced yield being obtained. This is thought to be due to the formation of a nitrite side product. This shows that it is possible to run the reactions at a lower oxygen concentration and achieve the same yield by employing 20 mol% nitric acid.

Once the system had been optimised and tested for a selection of secondary activated and unactivated alcohols, the optimised reaction conditions were repeated in various ionic liquids. The ionic liquid was to be used as a replacement for the organic solvent, with the aim of immobilising the radical within the ionic liquid. This would allow the radical to be recycled, as the product could be removed at the end of the reaction, whilst the radical remained in the ionic liquid for reuse. As previously highlighted ionic liquids can be a good alternative to traditional organic solvents due to their negligible vapour pressure. This is especially advantageous when carrying out oxidative reactions, as this negates any flammability concerns.

Ionic liquids with the bistriflimide $[\text{Tf}_2\text{N}]$ and tris(pentafluorethyl)trifluorophosphate [FAP] anions were chosen to allow for

low viscosity and high thermal stability of the ionic liquid. It was also desirable to choose ionic liquids with weakly co-ordinating anions, as dichloromethane is the traditional solvent for NO_x based reactions. In addition, it is known that weakly co-ordinating anions are favoured as these result in increased stability of the oxoammonium cation.⁵⁵ The selected ionic liquids can be seen in Figure 2.39.

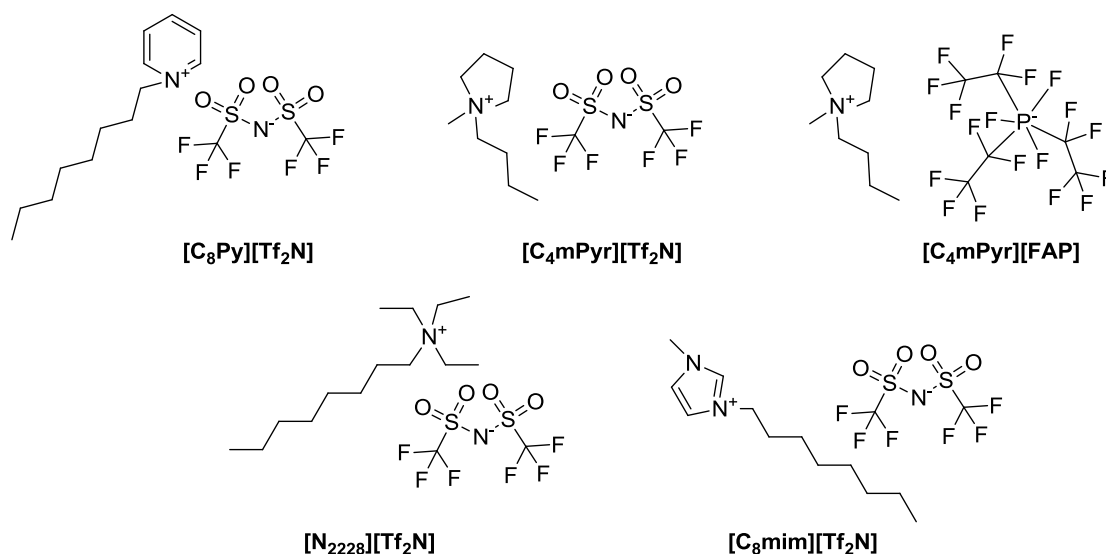


Figure 2.39 Selected ionic liquids for screening.

The ionic liquids were compared using both previously mentioned gas compositions; 40 bar air and 40 bar 8% O_2/N_2 , and as seen in Figure 2.40 negligible difference was observed across all five ionic liquids with the two different gas compositions. The best results were obtained when using the 1-butyl-1-methylpyrrolidinium cation in combination with both the FAP and Tf_2N anions. Note that in the case of the ionic liquid system, all results are reported as % conversion, rather than % yield. Within the acetonitrile system, biphenyl was added to the reaction solution at the end of the reaction and stirred to fully dissolve before a sample was taken for GC analysis. It was necessary to add the standard at the end of the reaction, as when added at the start biphenyl was found to react with the NO_x . In the case of the ionic liquid it was more difficult to ensure all the biphenyl had dissolved when added at the end of the

reaction, and so an initial check was carried out as follows. The reaction was run and then diluted with 3 mL ether, and biphenyl added, and left to stir and dissolve. The yield and conversion were then calculated and found to be within error of each other. This shows that there are no side products being formed in the reaction, and so conversion by GC is an accurate way of comparing results.

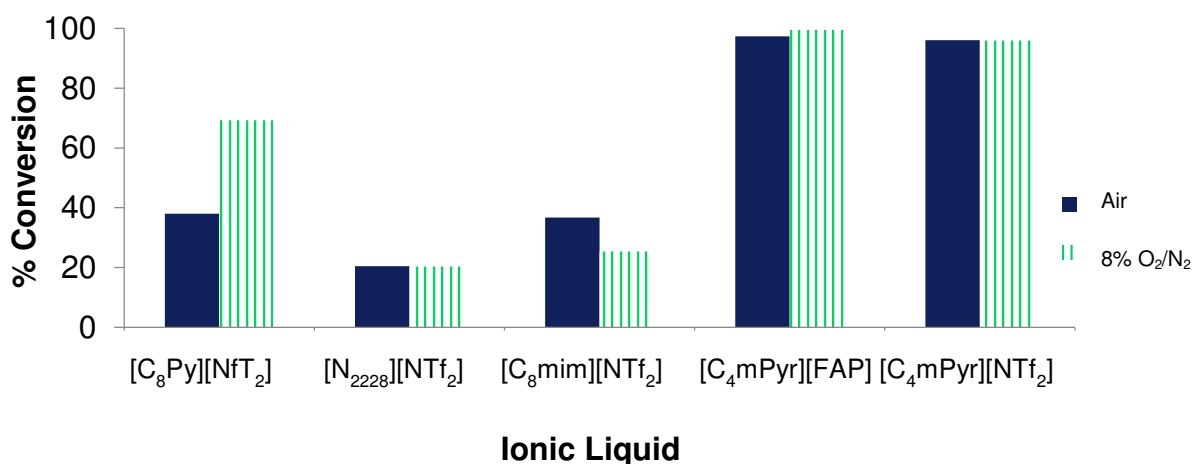


Figure 2.40 Ionic liquid screen under varying gas composition.

Reaction conditions; 2-octanol (1 mmol), nitric acid (10 mol%), TEMPO (5 mol%), 1 mL ionic liquid, 4 h, 60 °C, 500 rpm, 40 bar X.

The [C₄mPyr][FAP] ionic liquid was chosen to carry out the same substrate scope as previously performed in acetonitrile with both TEMPO and ABNO. As seen in Figure 2.41 and 2.42, almost identical results were achieved in the ionic liquid system to that in the previous acetonitrile system, with the exception of menthol, which saw an increase in the conversion obtained when in the ionic liquid.

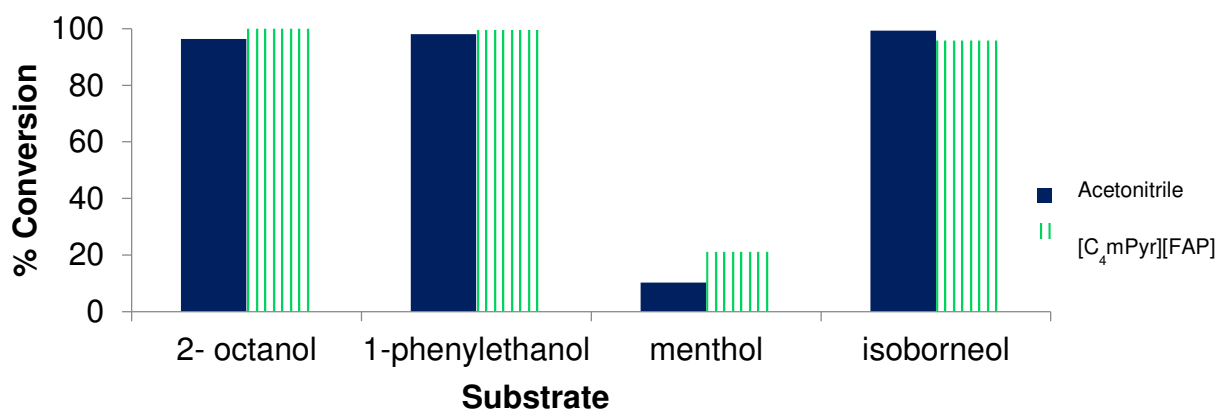


Figure 2.41 Substrate scope with TEMPO comparing acetonitrile and [C₄mPyr][FAP].

Reaction conditions; Substrate (1 mmol), TEMPO (5 mol%), nitric acid (10 mol%), solvent (1 mL), 60 °C, 4 h, 40 bar 8% O₂/N₂, 500 rpm.

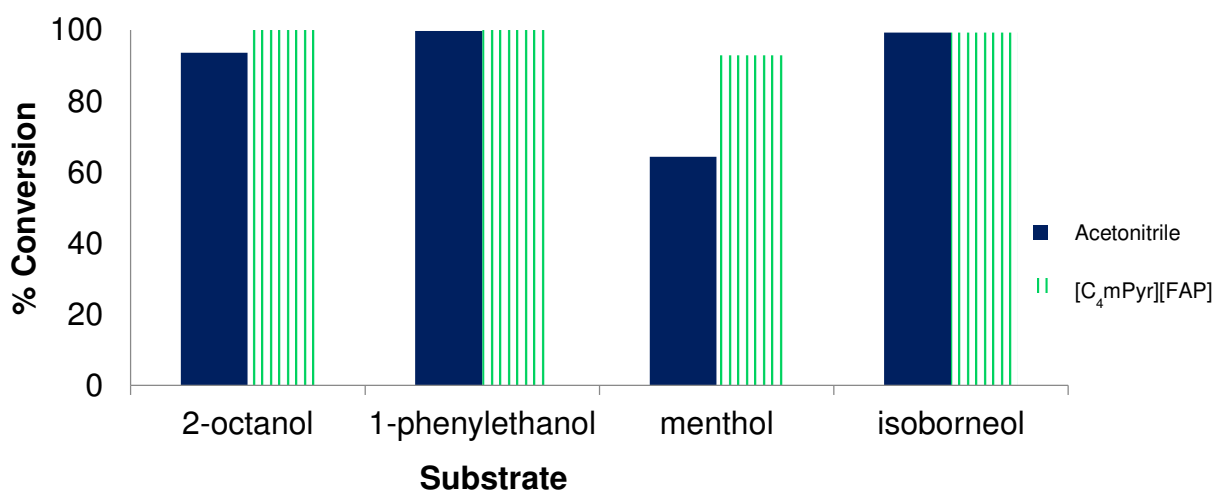


Figure 2.42 Substrate scope with ABNO comparing acetonitrile and [C₄mPyr][FAP].

Reaction conditions; Substrate (1 mmol), ABNO (5 mol%), nitric acid (10 mol%), solvent (1 mL), 60 °C, 4 h, 40 bar 8% O₂/N₂, 500 rpm.

Initially it was not clear if the increase in reactivity observed with menthol was a result of an increase in concentration when moving from acetonitrile to the ionic liquid or due to a positive effect of the ionic liquid itself. In order to study this further, menthol was run using both TEMPO and ABNO in three different

solvent systems, including an alternative ionic liquid, $[C_4mPyr][Tf_2N]$. The results can be seen in Figure 2.43.

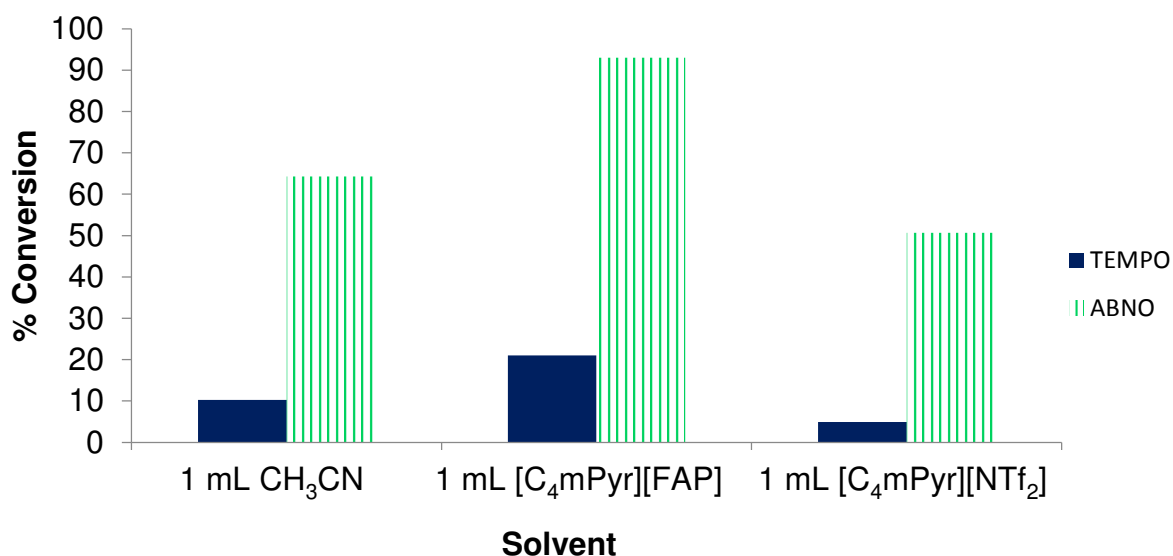


Figure 2.43 Study of menthol in different solvents.

Reaction conditions; menthol (1 mmol), radical (5 mol%), nitric acid (10 mol%), solvent, 60 °C, 4 h, 40 bar 8% O₂/N₂, 500 rpm.

As can be seen, there is a decrease in yield when moving from acetonitrile to $[C_4mPyr][Tf_2N]$. As this would be of similar concentration to $[C_4mPyr][FAP]$, it confirms that the effect observed is due to a property of the $[C_4mPyr][FAP]$ ionic liquid itself.

Having found a system that worked with equal, if not better efficiency when using an ionic liquid, $[C_4mPyr][FAP]$, as the solvent, it was initially thought that it may be possible to distill the product off under vacuum, leaving the TEMPO radical immobilised within the ionic liquid. Theoretically the ionic liquid could then be charged with fresh substrate and cheap, abundant nitric acid, before being used again. For the initial testing of the distillation, benzyl alcohol was chosen as the model substrate, as it was thought that it could be distilled off more easily than 2-octanol. Unfortunately, even with heating at 60 °C, a high vacuum was required to remove the product, and even under these conditions, it was not possible to remove the entire product. This led us to believe that if

distillation of benzaldehyde could not be achieved under these conditions, menthone (a highly desirable molecule in both the flavour and fragrance industry) distillation would not be possible, therefore making this an unsuitable method of catalyst recycling.

As previously mentioned, there are many potential benefits to employing an ionic liquid in the reaction system, such as enhancing reactivity, or their negligible vapour pressure. However, ionic liquids are expensive to synthesise, and are required in large volumes when being applied as a solvent alternative to traditional organics. In addition, with regards to oxidation reactions, it is possible that mass transfer problems may arise as the ionic liquid viscosity increases. As highlighted earlier, the application of SILPs (supported ionic liquid phase) may alleviate these problems. The use of a SILP allows for a smaller quantity of ionic liquid. This has a two-fold advantage; firstly less ionic liquid is economically beneficial, but also the thin layer reduces the risk of mass transfer limitations.

In this study it was thought that the TEMPO and 1-butyl-1-methylpyrrolidinium tris(pentafluoroethyl)trifluorophosphate $[C_4mPyr][FAP]$, could be immobilised onto silica, to form a SILP. The reaction could then be run using non-polar hexane as the mobile phase, with nitric acid and substrate. This would allow for the reaction to occur within the ionic liquid, as with the homogeneous system, however should also enable catalyst recycling as the catalyst could be filtered off after the reaction, and washed with hexane before re-use.

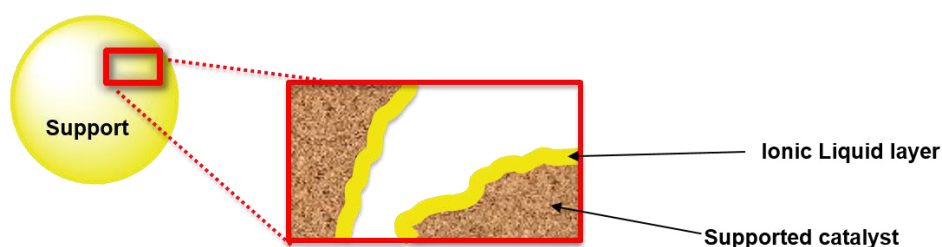


Figure 2.44 Representation of SILP structure.

We wished to ensure that the $[\text{C}_4\text{mPyr}][\text{FAP}]$ ionic liquid remained the best suited ionic liquid when applied heterogeneously, and so it was screened against the two other highest yielding ionic liquids from the homogeneous screen. These were $[\text{C}_8\text{Py}][\text{NfT}_2]$ and $[\text{C}_4\text{mPyr}][\text{NTf}_2]$. In line with the bulk ionic liquid results, the SILP prepared with $[\text{C}_4\text{mPyr}][\text{FAP}]$ gave the best performance when tested with both 1-phenylethanol and 2-octanol. Further optimisation was carried out to determine the loading of ionic liquid per gram of silica when preparing the SILP. It was found that 0.2 g of $[\text{C}_4\text{mPyr}][\text{FAP}]$ per gram of silica gave the optimum results. Once the SILP had been optimised, we tested it under the previously optimised reaction conditions. However, we wished to compare 5 mol% and 10 mol% TEMPO catalyst loadings, as it was anticipated that the heterogeneous system may be less reactive than the homogeneous system. The results obtained can be seen in Figure 2.45. Again as with the bulk ionic liquid system the results are reported as conversion. A check was performed this time with dodecane as an internal standard due to the use of hexane as the reaction solvent. As previously, the conversion and yield were found to be within error.

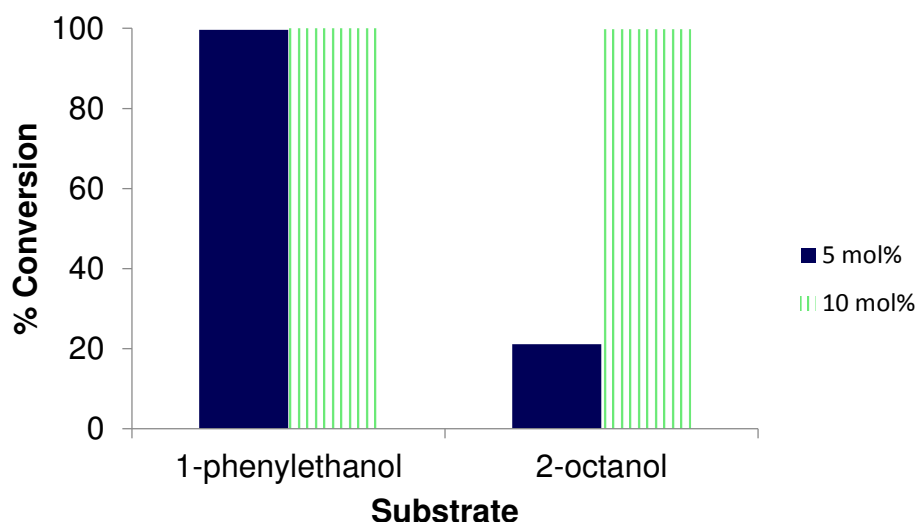


Figure 2.45 Comparison of catalyst loading with 1-phenylethanol and 2-octanol.

Reaction conditions; substrate (1 mmol), TEMPO SILP (0.156 g or 0.313 g equating to 5 mol% or 10 mol% TEMPO respectively), nitric acid (10 mol%), hexane (3 mL), 40 bar air, 24 h, 60 °C, 500 rpm.

As can be seen from the graph above, it was deemed necessary to increase the catalyst loading to 10 mol% to achieve high yields with aliphatic substrates. We believe the reason for this is the additional phase boundary on the heterogeneous catalyst, which therefore results in a slower reaction. This is therefore amplified when using less reactive substrates i.e. aliphatic alcohols. An additional reason may be the preferential partitioning of the substrate between the layers. It could be suggested that 1-phenylethanol prefers to be in the ionic liquid layer, however 2-octanol has a preference for the hexane mobile phase. This would mean that in the case of 1-phenylethanol, there is a higher substrate concentration within the ionic liquid layer, leading to an increase in reactivity. A 10 mol% catalyst loading was then compared under various gas mixtures, 8 % O₂/ N₂, and compressed air. These reactions were run in a shorter time of four hours, in order to allow the difference in reactivity (should there be one) to be observed.

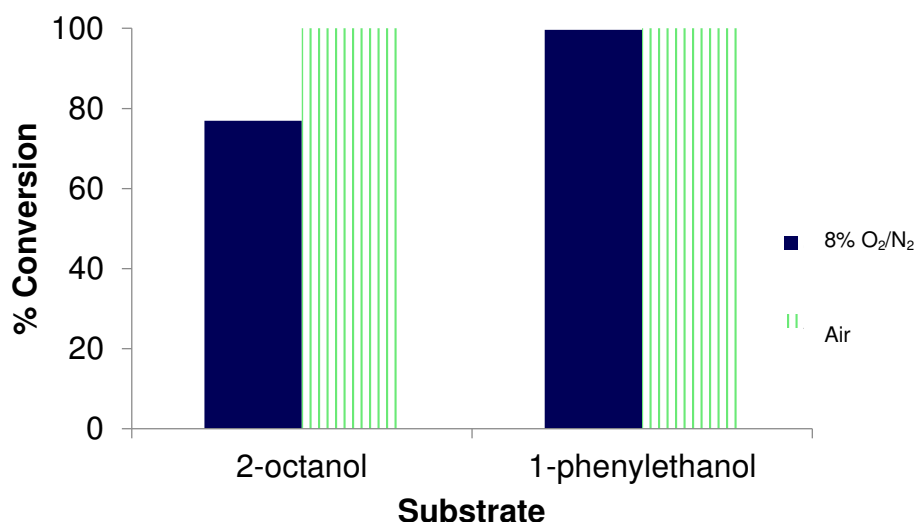


Figure 2.46 Comparison between different gas compositions.

Reaction conditions; substrate (1 mmol), SILP catalyst (10 mol% TEMPO with 0.2 g of [C₄mPyr][FAP] per gram of silica), nitric acid (10 mol%), hexane (3 mL), 60 °C, 4 h, 40 bar gas, 500 rpm.

As can be seen, no difference in reactivity is observed between the two gas compositions for 1-phenylethanol, however with 2-octanol, a difference in reactivity of approximately 20 % is observed. This is in accordance with what was observed in the homogeneous system. Aliphatic substrates exhibit a lower yield when under lower pressures of oxygen due to the complex equilibria that involve the formation of nitrites with less reactive alcohols.

The SILP was then tested for its recycling potential using 2-octanol. Once the reaction had been run, the SILP was filtered from the reaction mixture under vacuum, and washed several times with hexane. The SILP was then charged with fresh nitric acid and substrate and the reaction was run again. Unfortunately, the conversion went from 100 % on the first run to less than 5% on the second, showing that the catalyst in this form cannot be recycled. It is thought that this may be due to the TEMPO catalyst leaching from the SILP during the reaction, into the hexane, which is then lost during filtration. It was thought that this perhaps could be prevented by using sulfonated TEMPO as a replacement for TEMPO. The sulfonated TEMPO could be used as the anion for the ionic liquid, thus preventing the need for additional ionic liquid.

The SILP (herein shall be referred to as the SULFOSILP/ sulfonated SILP) was prepared by making the ionic liquid, $[N_{4444}][C_9H_{17}NO_3S]$ (Figure 2.47) *in situ* by reacting $[N_{4444}][OH]$ with sulfonated TEMPO in acetonitrile and methanol, whilst coating onto the silica.

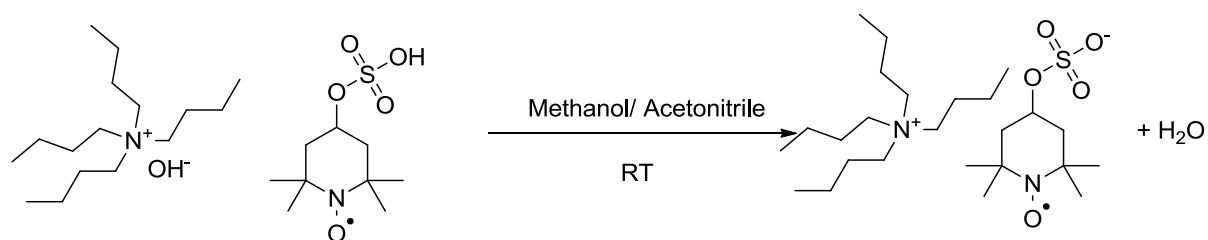


Figure 2.47 Sulfonated SILP synthesis.

A 10 mol% catalyst loading of sulfonated TEMPO was chosen and then compared to the reactivity of the previous TEMPO SILP. It was found that the sulfonated SILP was less reactive than the TEMPO SILP in the case of less reactive aliphatic substrates as can be seen in Figure 2.48.

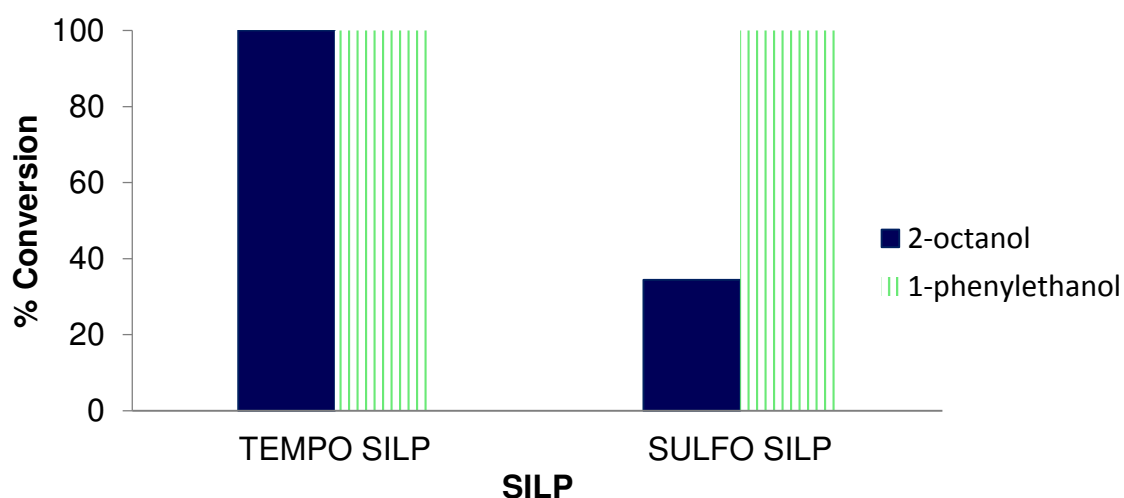


Figure 2.48 Comparison of SILPs with different substrates.

Reaction conditions; substrate (1 mmol), SILP (10 mol%), nitric acid (10 mol%), hexane (3 mL), 40 bar air, 4 h, 60 °C, 500 rpm.

Despite showing a lower reactivity to the original SILP system, the sulfonated SILP was tested for its recycling potential. As previously, the solid catalyst was filtered from the reaction mixture at the end of the reaction, then charged with fresh nitric acid and substrate and re-run. Unfortunately, the same results were observed as previously, experiencing a decrease from 100 % conversion to less than 5 % in the second run. This indicates that there are two possible things happening in the reaction, either the reaction conditions are resulting in a death of the catalyst in the first run, or catalyst leaching is still occurring.

It is possible that the problems associated with recycling the SILP system may still be due to catalyst leaching from the ionic liquid phase to the mobile hexane phase. In an attempt to circumvent this problem, covalently tethered silica-TEMPO was tested. Silica tethered TEMPO was synthesised by repeating a commonly used literature process whereby the 3-aminopropyltriethoxysilane is tethered to silica, in toluene under a nitrogen atmosphere. 4-oxo-TEMPO is then added *via* reductive amination, to form the immobilised silica catalyst.³⁹

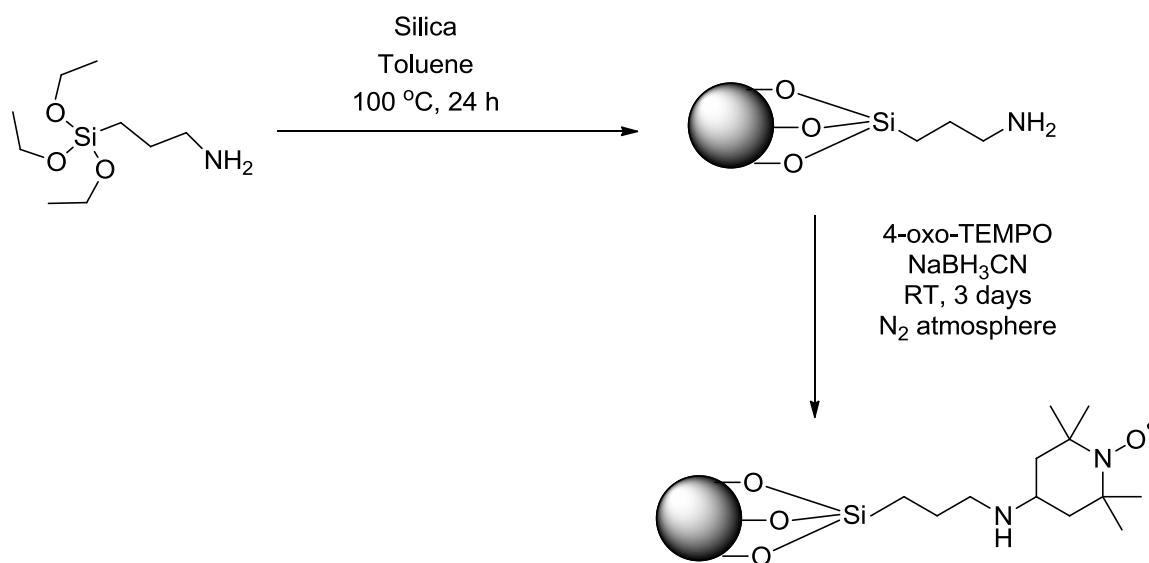


Figure 2.49 Synthesis of silica tethered TEMPO.³⁹

Once synthesised the catalyst was tested under the previously optimised conditions; 5 mol% Si-TEMPO, 10 mol% nitric acid, acetonitrile, 40 bar air, 60 °C for 4 hours. Under these conditions, no activity was observed. It was initially thought that the high pressure may be problematic when using silica

tethered TEMPO as it has been shown that silica can be used as a method for trapping NO_x gas.⁵⁶ In order to evaluate if this was the issue, the silica TEMPO was tested using an oxygen balloon as an alternative to 40 bar air. This improved the obtained yield from 3% to 10%; however this is not comparable to results previously obtained in the literature.^{38,42} It has previously been reported that silica-TEMPO prepared *via* the chosen method can result in poor stability of the catalyst due to intramolecular quenching of the radicals that are anchored in close proximity at the surface of the material.⁵⁷

It is thought that a different method of synthesis, otherwise known as sol-gel synthesis can prevent this problem from occurring. Commercially available silica tethered TEMPO (SiliaCat TEMPO) is prepared *via* this method whereby firstly the 4-oxo-TEMPO undergoes reductive amination with 3-aminopropyltriethoxysilane to allow the formation of a functionalised silane, and then this is allowed to copolymerise with a suitable organosilane such as methyltriethoxysilane (MTES).⁵⁸ This results in the formation of an immobilised catalyst where the TEMPO molecules are homogeneously entrapped within the porosity of an organoceramic matrix. Commercially available silica-TEMPO was then tested under the previously optimised reaction conditions to give vastly improved results as can be seen in Figure 2.50.

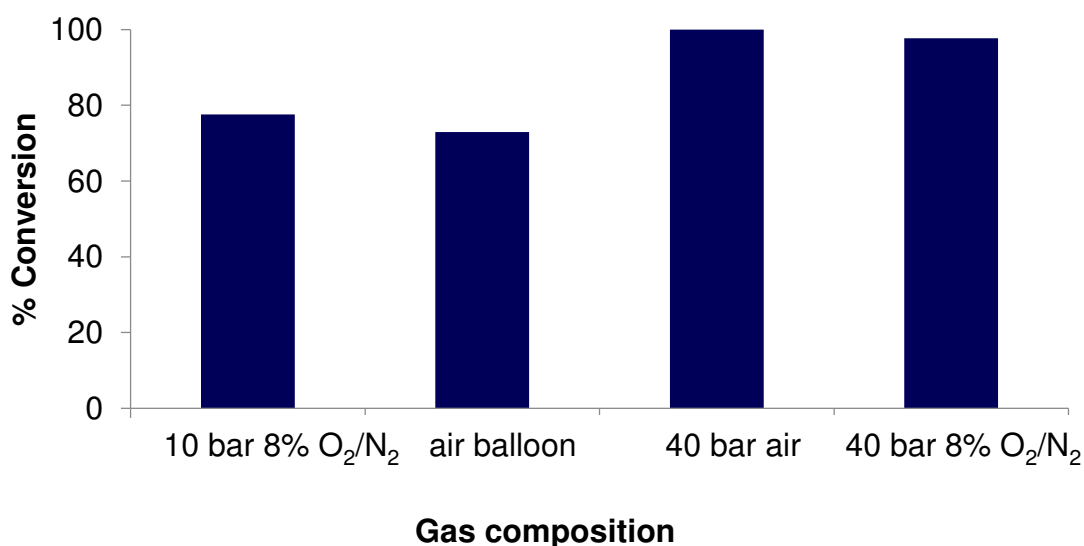


Figure 2.50 1-Phenylethanol with SiliaCat TEMPO under various gas compositions.

Reaction conditions; 1-phenylethanol (1 mmol), siliaCat TEMPO (5 mol%), nitric acid (10 mol%), acetonitrile (2 mL), gas, 4 h, 60 °C, 500 rpm.

As can be seen from the graph (Figure 2.50) high conversions to acetophenone could be achieved within four hours with *siliaCat* TEMPO under the previously optimised conditions. It was shown that the reaction was dependent on gas composition, as 40 bar air and the air balloon gave the best and poorest conversions respectively. Following from this 2-octanol was also tested under the same conditions as can be seen in Figure 2.51.

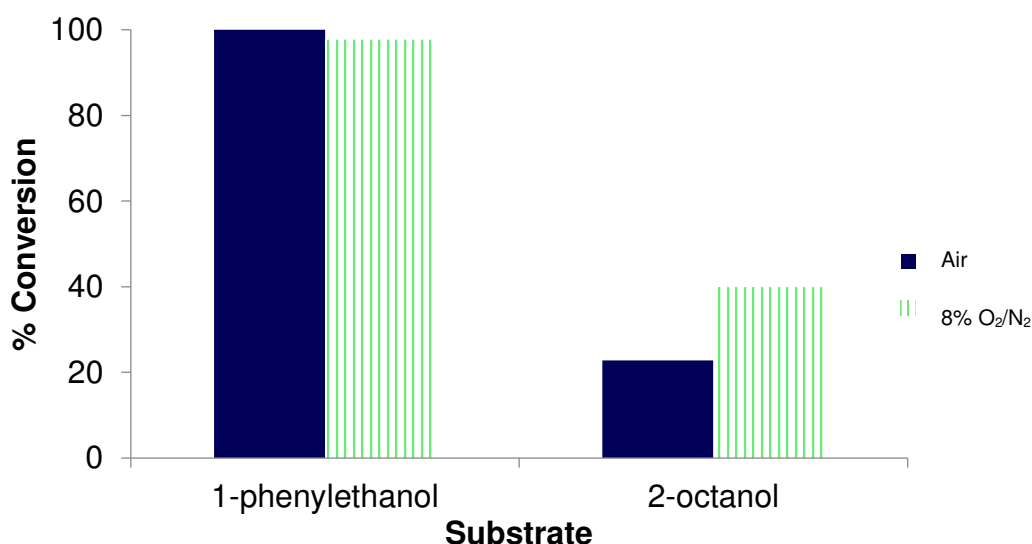


Figure 2.51 2-Octanol and 1-phenylethanol tested with *SiliaCat* TEMPO. Reaction conditions; Substrate (1 mmol), *siliaCat* TEMPO (5 mol%), nitric acid (10 mol%), acetonitrile (2 mL), gas (40 bar), 3 h, 60 °C, 500 rpm.

The results in Figure 2.51 demonstrate that 2-octanol can also be oxidised under the same conditions with *siliaCat* TEMPO, however the reaction is slower with the aliphatic alcohol. This is to be expected as the heterogeneous nature of the system causes a decrease in the rate of reaction, which is then amplified by the use of an aliphatic alcohol rather than the activated benzylic alcohol, 1-phenylethanol.

After the initial positive results, the sol-gel prepared *siliaCat* TEMPO was then tested for its recycling potential. This was tested by two different methods.

Initially, recycling potential was tested by running one substrate, 1-phenylethanol to achieve a conversion of 79%, then charging the same reaction mixture with a different substrate, 2-octanol and fresh nitric acid, to achieve a 23% conversion to 2-octanone, which correlates with results shown in Figure 2.51 for 2-octanol with *siliaCat* TEMPO on the first run. The catalyst was then also tested by running the reaction, and then filtering the catalyst from the reaction mixture, rinsing with acetonitrile and then used for a consecutive reaction with fresh substrate and nitric acid. The results can be seen in Figure 2.52.

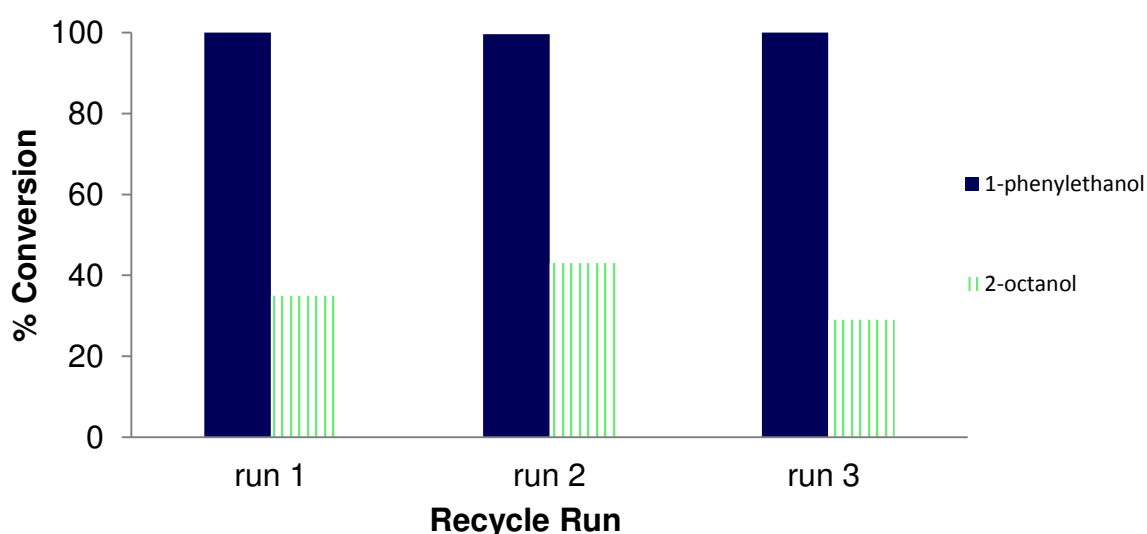


Figure 2.52 Recycling of *SiliaCat* TEMPO with 1-phenylethanol and 2-octanol.

Reaction conditions; Substrate (1 mmol), *siliaCat* TEMPO (5 mol%), nitric acid (10 mol%), acetonitrile (2 mL), 40 bar air, 3 h, 60 °C, 500 rpm.

As can be seen from the graph, very little loss in activity was observed when recycling the catalyst over three consecutive runs, for both 1-phenylethanol, and 2-octanol. It is also possible that the small loss in activity can be attributed to the loss of small amounts of catalyst when filtering the silica from the reaction mixture between runs.

These results support work previously shown in the literature; that *siliaCat* TEMPO is more stable than covalently tethered TEMPO prepared by the method of immobilising 3-aminopropyltriethoxysilane onto silica, and then

tethering TEMPO *via* reductive amination.⁵⁷ It is thought that siliaCat TEMPO is a more stable reactive catalyst as the entrapment within the silica gel matrix allows for higher physical and chemical stability of the TEMPO molecules, preventing the interactions between neighbouring TEMPO functional groups which can lead to partial catalyst degradation due to an oxoammonium ion mediated cleavage of amino bonds.⁵⁹

2.4 Conclusions

In conclusion, a metal free NO_x system has been developed that utilises nitric acid as a cheap practical sole source of NO_x . It has been demonstrated that this system can successfully oxidise secondary benzylic and aliphatic alcohols, including bulky substrates. The system was then tested in ionic liquids, to display activity of the same efficiency as with the acetonitrile system, however the radical could not be recycled by this method due to difficulties in separation. Two SILPs were then prepared using both TEMPO and sulfoTEMPO. As expected, these methods were much slower than the homogeneous system, and still did not allow for catalyst recycling due to either leaching of the catalyst, or catalyst deactivation during the reaction. In an attempt to solve this problem, immobilised radicals supported on silica were prepared. This particular means of immobilisation caused problems with catalyst stability. It was shown that through the use of sol-gel prepared *SiliaCat* TEMPO, these problems could be avoided, and the TEMPO could be used under the optimised reaction conditions and recycled up to three times without a loss in activity. Future work would include the preparation of a sol-gel containing ABNO, as this would allow for the recycling of radicals when oxidising bulkier substrates such as menthol.

In 2016, after the preparation of this chapter, Sheldon and co-workers devised a system that employed TEMPO with an ionic ammonium tag that could be carried out in $[\text{bmim}][\text{PF}_6]$ ionic liquid.⁶⁰ The theory was that ionic TEMPO would remain in the ionic liquid after the reaction to allow for facile recycling of the nitroxyl radical. The reaction conditions can be seen below in Figure 2.53.

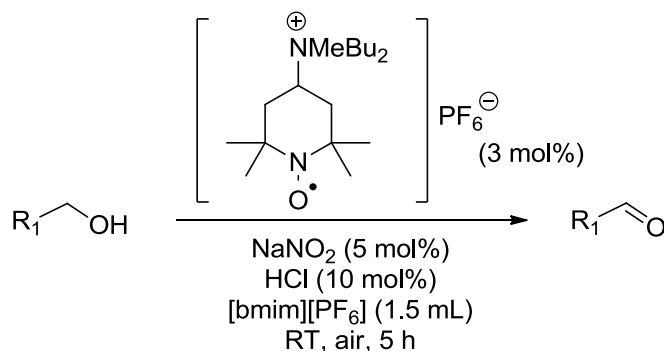


Figure 2.53 Oxidation with ionic TEMPO in $[\text{bmim}][\text{PF}_6]$.⁶⁰

Under the optimised conditions, primary and secondary aromatic and aliphatic alcohols exhibited a high activity. In addition, the ionic liquid containing the TEMPO catalyst could be reused up to five times without loss in activity.

This system draws several similarities with that reported within. The TEMPO radical employed is immobilised within the ionic liquid, due to the ionic tag, and can therefore be recycled – as was the aim in this chapter. Importantly, the cationic ammonium tag appears to play a key role in increasing the rate of oxidation, as a control experiment showed that the reaction with the individual components resulted in a reduced yield. In addition, it was found that the weakly co-ordinating PF_6^- anion showed not only an increased yield of aldehyde, but better recycling potential. This is in agreement with the results obtained with this chapter, that weakly co-ordinating anions were preferred. Contrastingly, the reaction was run at room temperature, rather than 60 °C, which may result in increased radical stability.

The system reported by Sheldon still requires both sodium nitrite and acid, in contrast to that reported here which uses only cheap nitric acid. In addition, the system was only demonstrated for use with simple alcohols, and was not expanded to those such as menthol. It would be interesting to explore this methodology with ABNO in order to expand the substrate scope.

2.5 Experimental

2.5.1 General Considerations

Unless otherwise stated, all reagents were purchased from Sigma-Aldrich and used without further purification. Air cylinder was from BOC and pre-mixed O₂:N₂(8:92) (β standard) cylinder was from BOC Special Gases. Ionic liquid 1-butyl-1-methylpyrrolodinium tris(pentafluoroethyl)trifluorophosphate (high purity) was received with thanks from Merck.

All synthesis and reactions were carried out in oven-dried glassware. Any reactions that were monitored by thin layer chromatography were carried out using Merck silica gel 60 sheets and visualised with UV light. Flash column chromatography was performed with 60 Å silica gel as the stationary phase, and all solvents used were of analytical grade.

¹H-NMR spectra were recorded on a Bruker AVX400 (400 MHz) spectrometer at room temperature. ¹³C NMR spectra were recorded on a Bruker AVX400 (100 MHz) spectrometer at room temperature. NMR data is reported as follows; chemical shift is recorded in parts per million (δ, ppm) in deuterated chloroform (CDCl₃) taken as 7.26 ppm. Multiplicity; s= singlet, d=doublet, dd= doublet of doublets, td= triplet of doublets, dt = doublet of triplets, m= multiplet.

Analysis of 2-octanol, isoborneol and menthol was performed by Gas Chromatography was performed using an Agilent 6890N series gas chromatograph. An Agilent 19091J-433 HP-5 5% Phenyl Methyl Siloxane capillary (column) (30.0 m x 250 μm x 0.25 μm nominal) was employed for all the separations using the following conditions. Column head pressure, 30 kPa (4.49 psi) helium; initial column temperature, 40 °C; initial hold time, 0 min; rate of temperature ramp 1, 4 °C/min; next temperature, 100 °C; hold time, 0 min; rate of temperature ramp 2, 30 °C/min, final temperature 320 °C; hold time, 15 min; injection temperature, 250 °C; detection temperature, 250 °C. The effluent was combusted in a H₂/Air flame and detected using an FID (flame ionisation detector). Ion count data were sent to a plotter, which integrated the area under the peaks.

Reactions with 1-phenylethanol were analysed using a 30 m × 0.32 mm ID SOLGEL-WAX 0.5UM (SGE Analytical Science) column under the following conditions: initial column temperature, 50 °C; initial hold time, 1 min, next temperature, 200 °C; hold time, 0 min; rate of temperature ramp 1, 25 °C/min, final temperature 230 °C; hold time, 18 min; rate of temperature ramp 2, 3 °C/min; injection temperature, 250 °C; detection temperature, 250 °C. The effluent was combusted in an H₂/ air flame and detected using a flame ionisation detector (FID). Ion count data were sent to a plotter, which integrated the area under the peaks.

The conversions and yields reported were calculated by GC using biphenyl or dodecane as an internal standard. An initial response factor (R_f) was calculated for the particular product or starting material, by dissolving a known amount of analyte and standard in ether. Then the following equation was used to calculate the R_f value:

$$R_f = \frac{\text{Moles}_{\text{analyte}} \times \text{Area}_{\text{internal standard}}}{\text{Moles}_{\text{internal standard}} \times \text{Area}_{\text{analyte}}}$$

The amount of product or starting material present was then calculated using the following equation:

$$\text{Moles}_{\text{analyte}} = \frac{\text{Moles}_{\text{internal standard}} \times R_f \times \text{Area}_{\text{analyte}}}{\text{Area}_{\text{internal standard}}}$$

2.5.2 General Methods

General Considerations

All reactions were carried out in 15 mL or 45 mL pressure vessels which were placed inside a pre-heated aluminium block, on a stirring hotplate. The heating block was thermostatically controlled during the reaction. Unless otherwise

stated, all reactions were carried out in a glass liner, with a Teflon coated 'rugby ball' stir bar. Reactions were cooled in an ice bath prior to sampling.

Example of Experimental Procedure for Optimisation in Acetonitrile

Reactions were performed in a 15 mL reactor body made of hastelloy and the reaction mixture was placed in a glass liner, equipped with a magnetic stirrer. To the glass liner was added TEMPO (5 mol%, 0.05 mmol, 7.8 mg), acetonitrile (1 mL) and nitric acid (10 mol%, 0.1 mmol, 0.006 mL) *via* microsyringe. The substrate was then added (1 mmol) and the reactor was sealed and pressurised with 40 bar of 8 % O₂/ N₂. The reactor was then stirred on a pre-heated block at 60 °C for four hours. Once the reaction was complete, the reactor was cooled in an ice bath and slowly depressurised in a fume hood. Internal standard (biphenyl) (~0.2 g) was added, and the glass liner magnetically stirred for 1 minute to ensure all standard was fully dissolved. A sample was then prepared for GC analysis by filtration through a silica plug with diethyl ether to remove any catalyst components. The sample was then submitted for GC analysis.

Example of Experimental Procedure for Optimisation in [C₄mPyr][FAP]

Reactions were performed in an 15 mL reactor body made of hastelloy and the reaction mixture was placed in a glass liner, equipped with a magnetic stirrer. To the glass liner was added, TEMPO (5 mol%, 0.05 mmol, 7.8 mg), [C₄mPyr][FAP] (1.5 g) and nitric acid (10 mol%, 0.1 mmol, 0.006 mL) *via* microsyringe. The substrate was then added (1 mmol) and the reactor was sealed and pressurised with 40 bar of 8 % O₂/ N₂. The reactor was then stirred on a pre-heated block at 60 °C for four hours. Once the reaction was complete, the reactor was cooled in an ice bath and slowly depressurised in a fume hood. A sample was then prepared for GC analysis by filtration through a silica plug with diethyl ether to remove any catalyst components. The sample was then submitted for GC analysis.

Example of Experimental Procedure for Optimisation utilising SILP

Reactions were performed in an 15 mL reactor body made of hastelloy and the reaction mixture was placed in a glass liner, equipped with a magnetic stirrer. To the glass liner was added, TEMPO SILP using [C₄mPyr][FAP] (0.156 g, 0.05 mmol, 5 mol%), hexane (3 mL), nitric acid (0.006 mL, 0.10 mmol, 10 mol%) *via* microsyringe and 2-octanol (0.130 g, 1 mmol). The reaction was pressurised to 40 bar with compressed air, and then stirred on a pre-heated block at 60 °C for twenty-four hours. Once the reaction was complete, a sample was prepared for GC analysis by filtration through a silica plug with diethyl ether.

Example of Experimental Procedure for Optimisation utilising SiliaCat TEMPO

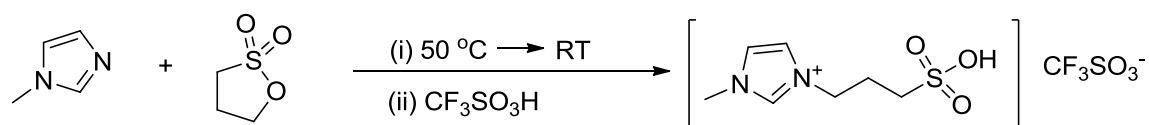
Reactions were performed in an 15 mL reactor body made of hastelloy and the reaction mixture was placed in a glass liner, equipped with a magnetic stirrer. To the glass liner was added, SiliaCat TEMPO (0.071 g, 0.05 mmol, 5 mol%), acetonitrile (1 mL), nitric acid (0.006 mL, 0.10 mmol, 10 mol%) *via* microsyringe and substrate (1 mmol). The reaction was pressurised to 40 bar with compressed air, and then stirred on a pre-heated block at 60 °C for four hours. Once the reaction was complete, a sample was prepared for GC analysis by filtration through a silica plug with diethyl ether.

Recycling of SiliaCat TEMPO

The reaction was performed as stated in the above example experimental procedure and then filtering the catalyst from the reaction mixture, rinsing with acetonitrile and then used for a consecutive reaction with fresh substrate and nitric acid.

2.5.3 Synthesis of Ionic Liquids

Synthesis of 1,-(3-sulfopropyl)-3-methylimidazolium triflate

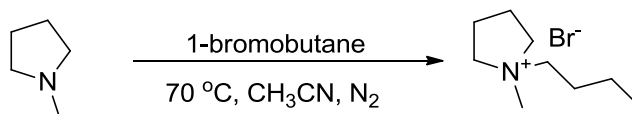


N-methylimidazole (0.45 moles, 37.43 g) was dissolved in acetonitrile (150 mL) in a 500 mL round bottomed flask, and stirred in an ice bath. 1,3-propanesultone (0.45 moles, 55.68 g) was dissolved in toluene (30 mL) and added dropwise *via* a dropping funnel to the *N*-methylimidazole solution over a time period of one hour. The ice bath was then removed and the solution left to stir at room temperature for a further two hours. A white precipitate was observed, and was left to cool in an icebath overnight. The precipitate was then filtered under vacuum and washed multiple times with diethyl ether.

The zwitterion (0.033 moles, 6.92 g) was dissolved in distilled water (50 mL) in a 250 mL round bottomed flask equipped with a magnetic stirrer. Trifluoromethane sulfonic acid (0.033 moles, 3 mL) was added slowly to the round bottomed flask, dropwise over several minutes. The reaction mixture was stirred at room temperature for one hour, followed by stirring at 70 °C for a further three hours. The reaction was then allowed to cool to room temperature and stirred overnight. The reaction solution was then concentrated under reduced pressure to yield an orange/ brown viscous liquid. The ionic liquid was dried under vacuum at 60 °C before use.

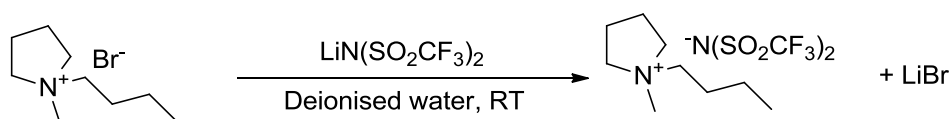
¹H NMR (300 MHz, D₂O): δ 8.51 (s, 1 H), 7.33-7.26 (t, *J*= 1.7 Hz, 1H), 7.25-7.20 (t, *J*= 1.6 Hz, 1H), 4.18-4.08 (t, *J*= 7.1 Hz, 2H), 3.67 (s, 3H), 2.74-2.65 (m, 2H), 2.14-2.01 (m, 2H). ¹³C-NMR (101 MHz, D₂O); δ 136.4, 124.1, 122.5, 48.1, 47.6, 36.0, 25.4. NMR obtained was in accordance with the literature.⁶¹

Synthesis of 1-butyl-1-methylpyrrolidinium bistriflimide



N-methylpyrrolidine (122.0 mL, 1.17 moles) and 1-bromobutane (138.5 mL, 1.29 moles) were dissolved in acetonitrile and refluxed under a nitrogen atmosphere for 42 hours. The reaction mixture was then cooled down slowly, and ethyl acetate added to recrystallize the [C₄mPyr][Br] salt. The salt was then filtered under vacuum and dried under reduced pressure. The salt was then dried under high vacuum overnight at 60 °C to give a white solid.

¹H NMR (300 MHz, DMSO): δ 3.55-3.40 (m, 4 H), 3.37-3.32 (m, 2H), 2.99 (s, 3H), 2.07 (bs, 4H), 1.74- 1.58 (m, 2 H), 1.36- 1.23 (dt, *J*= 7.3, 14.6 Hz, 2H), 0.98 -0.85 (t, *J*= 7.3 Hz, 3H).



1-butyl-1-methyl pyrrolidinium bromide (29.9 g, 0.135 moles) was dissolved in deionized water in a 500 mL conical flask equipped with a stirrer bar. Lithium bistriflimide (42.5 g, 0.148 moles) was weighed into a glass beaker and dissolved slowly in deionised water (100 mL). The lithium bistriflimide solution was then added to the [C₄mPyr][Br] solution slowly, with stirring. Once all the lithium bistriflimide solution was added, the reaction was left to stir at room temperature for sixteen hours. The lithium bromide was then removed by repeatedly washing the ionic liquid with deionised water, until no more bromide could be detected by the silver nitrate test. The solution was then washed a further three times. The ionic liquid was then dried under reduced pressure, and heated under high vacuum at 60 °C overnight.

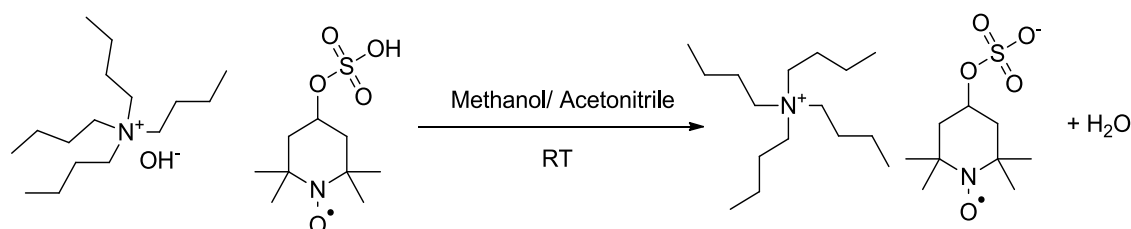
^1H NMR (300 MHz, DMSO): δ 3.57-3.40 (t, J = 8.8 Hz, 4H), 3.36-3.26 (m, 2H), 3.00 (s, 3H), 2.20-2.08 (m, 4H), 1.79-1.64 (m, 2H), 1.42-1.27 (m, 2H), 1.01-0.90 (t, J =7.3 Hz, 3H). ^{13}C -NMR (101 MHz, DMSO); δ 126.5, 112.2, 118.0, 113.7, 64.10, 48.0, 30.6, 25.5, 21.5, 19.7, 13.4. The NMR obtained was in accordance with the literature.⁶²

2.5.4 Synthesis of SILPS

Synthesis of TEMPO SILP- example using $[\text{C}_4\text{mPyr}][\text{FAP}]$

Silica (davisil) (2 g) and $[\text{C}_4\text{mPyr}][\text{FAP}]$ (0.4 g) were dried under high vacuum overnight at 130 °C and 60 °C respectively. After cooling under a nitrogen atmosphere, silica (2 g), $[\text{C}_4\text{mPyr}][\text{FAP}]$ (0.4 g) and TEMPO (0.1 g) were added to a 50 mL round bottomed flask and dissolved in dichloromethane (15 mL). The reaction was stirred at room temperature for three hours, and then the solvent removed under reduced pressure, before drying the solid SILP under high vacuum. The product appeared as a pale orange solid.

Synthesis of Sulfonated SILP

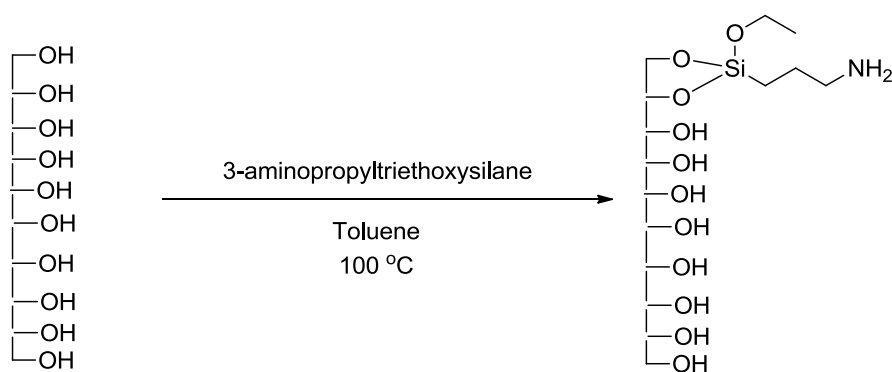


Silica (2 g) was dried under high vacuum overnight at 130 °C. After cooling under a nitrogen atmosphere, silica, $[\text{N}_{4444}][\text{OH}]$ in methanol (0.79 mL), and sulfonated TEMPO (0.2 g), were added to a round bottomed flask and dissolved in 10:1 acetonitrile: methanol (25 mL). The reaction was stirred at room temperature for three hours, and then the solvent removed under

reduced pressure, before drying the solid SILP under high vacuum. The product appeared as a pale yellow solid.

2.5.5 Synthesis of Covalently Tethered TEMPO

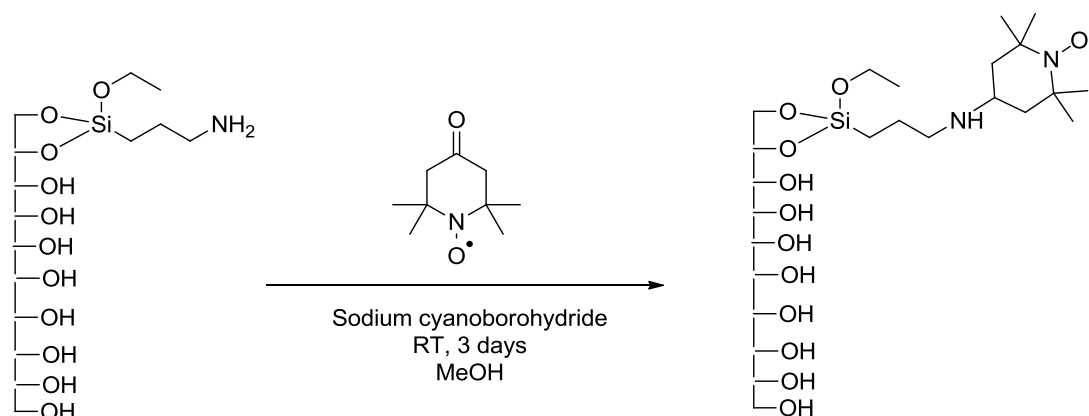
Functionalisation of silica gel



Silica gel (10 g) was pre-dried under high vacuum at 130 °C overnight, in an oven-dried 250 mL two-necked round bottomed flask equipped with a magnetic stirrer. Dry toluene (80 mL) was added followed by 3-aminopropyltriethoxysilane (11 mmol, 2.58 mL). The mixture was heated to 100 °C, with stirring under a nitrogen atmosphere for 24 hours. The silica was then filtered under vacuum and washed with toluene, before drying under high vacuum. After this time, CHN analysis showed quantitative addition of the 3-aminopropyltriethoxysilane.

CHN analysis: calculated (found) C; <5% (3.66%), H; <2% (0.82%), N; <2% (1.06%)

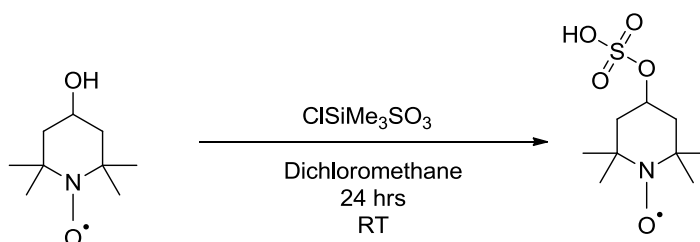
Synthesis of silica tethered TEMPO



The silica TEMPO was prepared in accordance to a literature procedure.³⁹ The dry silica (3 g) was then added to a 2-necked round bottomed flask equipped with a magnetic stirrer and placed under a nitrogen atmosphere. 4-oxo-TEMPO (3.75 mmol, 0.638 g) and sodium cyanoborohydride (30 mmol, 1.885 g) were then dissolved in methanol (20 mL) and the reaction was stirred for three days at room temperature. After this time the silica was filtered under vacuum and washed consecutively with toluene, hexane and dichloromethane. The silica was then dried under high vacuum before use. CHN analysis: calculated (found) C; <12.6 % (8.40%), H; 2.3% (1.21%), N; 2.7% (2.16%) This indicated a loading of 0.35 mmol/ g of TEMPO on the silica.

2.5.6 Synthesis of Nitroxyl Radicals

Synthesis of 4-sulfonatooxy-2,2,6,6-tetramethylpiperidine-1-yloxy

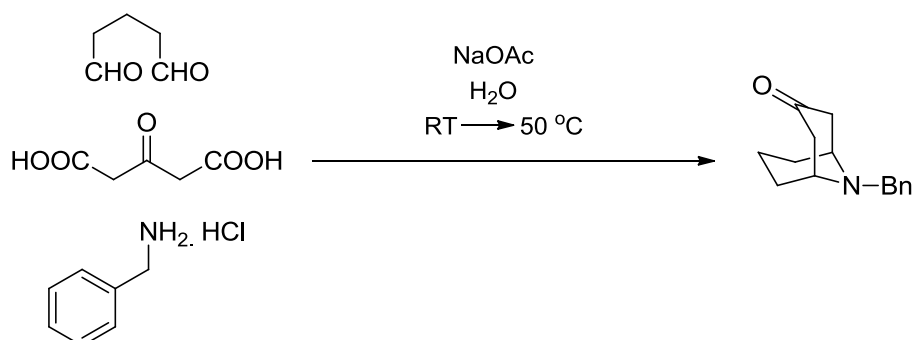


Sulfonated TEMPO was prepared in accordance to a literature procedure.⁶³ 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl (5.167 g, 30 mmol) was weighed into an oven dried 2-necked round bottomed flask equipped with a magnetic stirrer and dissolved in 150 mL of dichloromethane. Chlorosulfonic acid trimethylsilyl ester (1.9 mmol, 6 mL) was dissolved in 40 mL of dichloromethane, and 38 mL of this solution was added dropwise over fifteen minutes at 0 °C under a nitrogen atmosphere to the solution of 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl. The mixture was then left to stir for sixteen hours at room temperature. After this time, the product appeared as a yellow precipitate in an orange solution. The precipitate was then filtered under vacuum and washed with cold dichloromethane. The filtrate was then dried under high vacuum. The product appeared as a yellow crystalline solid, 6.75 g, 89% yield.

CHN analysis: calculated (found) C; 42.84% (40.94%), H; 7.19% (7.12%), N; 5.55% (5.43%), S; 12.71% (12.64).

HRMS (ESI⁺) Calc. for $\text{C}_9\text{H}_{19}\text{NSO}_5$ [M+H⁺] 252.0906, found: 252.0911.

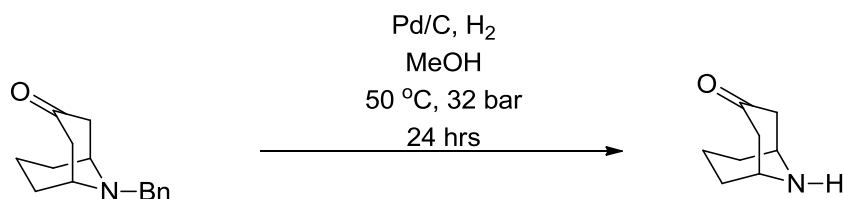
Synthesis of 9-benzyl-9-azabicyclo[3.3.1]nonane-3-one



9-Benzyl-9-azabicyclo[3.3.1]nonane-3-one was synthesised according to a literature procedure.³⁵ Benzylamine hydrochloride (37.7 g, 0.263 moles) and glutaraldehyde (88 mL, 25% in water, 0.219 moles) were added to an oven dried 500 mL round bottomed flask equipped with a magnetic stirrer and the mixture was cooled to 0 °C in an ice bath. Acetonedicarboxylic acid (32 g, 0.146 moles) and 10% aqueous sodium acetate (75 mL) were then added to the reaction mixture, the ice bath was removed and the solution was stirred for two hours at room temperature. The solution was refluxed at 50 °C for eighteen hours. The mixture was cooled to room temperature and the pH adjusted to pH 7 by the addition of sodium hydrogencarbonate solution. The organic product was then extracted multiple times with chloroform to produce a dark brown organic layer. The organic layer was washed with brine and dried over anhydrous sodium sulphate. The filtered organic layer was then concentrated under reduced pressure to give a dark brown oil. The oil was filtered over a short pad of silica gel, using hexane/ethyl acetate (3:2) as the eluent. The filtrate was then concentrated on the rotary evaporator to yield a dark golden yellow oil, which crystallised to produce a dark yellow crystalline solid in a 24.5% yield (12.32 g, 0.054 moles).

¹H NMR (300 MHz, CDCl₃): δ 7.40-7.20 (m, 5H), 3.91 (s, 2H), 3.32 (bs, 2H), 2.75-2.65 (dd, *J* = 16.6, 6 Hz, 2H), 2.30-2.20 (d, *J* = 16.7 Hz, 2H), 2.03-1.87 (m, 2H), 1.60-1.43 (m, 4H). ¹³C NMR (101 MHz, CDCl₃): δ 212.0, 139.6, 128.8, 128.7, 127.6, 57.5, 53.9, 43.3, 29.7, 17.0. NMR data was in accordance with the literature.³⁵

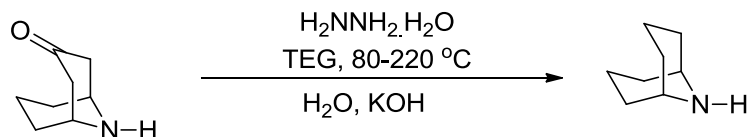
Synthesis of 9-azabicyclo[3.3.1]nonane-3-one



9-Azabicyclo[3.3.1]nonane-3-one was synthesised according to a literature procedure.³⁵ Ethyl acetate (20 mL) was placed in an oven-dried two necked round bottomed flask, sealed with a rubber septum and was bubbled through with nitrogen gas for an hour. 9-benzyl-9azabicyclo[3.3.1]nonan-3-one (5 g, 0.022 moles) was dissolved in the minimum volume of methanol (30 mL) in an oven-dried round bottomed flask and also bubbled through with nitrogen for an hour. Pd/C catalyst (1.16 g) was weighed into a 100 mL reactor body and covered with 20 mL of degassed ethyl acetate to form a catalyst 'slurry'. The reactor vessel was then sealed and flushed three times with nitrogen gas. The reaction mixture (substrate and methanol) was then syringed into the reactor *via* the injection valve and the reactor was flushed for a final time with nitrogen gas. The vessel was flushed twice with hydrogen gas before pressurising the reactor to 32 bar with hydrogen gas, and heating at 50 °C with stirring for twenty-four hours. After the reaction was complete the reactor was left to cool to room temperature and then degassed slowly before opening the vessel. The black slurry reaction mixture was then filtered over a celite plug with 3:1 ethyl acetate to methanol to produce a pale yellow solution. This was then concentrated under reduced pressure to yield a golden yellow oil that was then dried under vacuum for several hours to give a golden yellow solid in a 61% yield. (2.47 g, 0.017 moles).

¹H NMR (300 MHz, CDCl₃): δ 3.64 (bs, 2H), 2.70-2.58 (m, 2H), 2.43 (d, *J*=16.4 Hz, 2H), 1.91-1.46 (m, 7H). NMR data was in accordance with the literature.³⁵

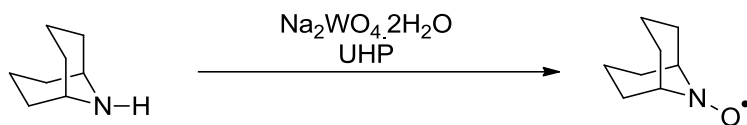
Synthesis of 9-azabicyclo[3.3.1]nonane



9-Azabicyclo[3.3.1]nonane was synthesised according to a literature procedure³⁵ and carried out by Laura Dornan. 9-azabicyclo[3.3.1]nonane (3 g, 21.5 mmol) was added to a 250 mL 3 necked round bottomed flask equipped with a magnetic stirrer. Hydrazine hydrate (3.3 mL, 64.5 mmol, 3 equiv.) was slowly added and the reaction mixture was heated to 80 °C for 2 hours. After this time the reaction mixture was allowed to cool to room temperature and distillation apparatus attached. Potassium hydroxide (12 g, 215 mmol, 10 equiv.) was added followed by 31 mL of triethylene glycol. The mixture was heated to 220 °C for 30 minutes before 150 mL of water was added dropwise over a period of 3 hours. The water distillate was extracted with chloroform several times and dried with potassium carbonate to yield a yellow oil, 0.94 g, 35%.

¹H NMR (300 MHz, CDCl₃): δ 3.10 (s, 2H), 2.14-1.95 (m, 2H), 1.96-1.81 (m, 4H), 1.75-1.55 (m, 6H). NMR data was in accordance with the literature.³⁵

Synthesis of 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO)



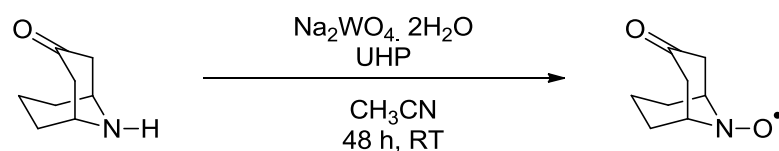
9-Azabicyclo[3.3.1]nonane *N*-oxyl was synthesised according to a literature procedure³⁵ and carried out by Laura Dornan. To a 250 mL round bottomed flask equipped with a stirrer bar was added 9-azabicyclo[3.3.1]nonane (1.33 g, 10.62 mmol) in 20 mL acetonitrile. Sodium tungstate dihydrate (0.351 g, 1 mmol) was added to the flask followed by slow addition of urea hydrogen peroxide (3 g, 32 mmol). The reaction mixture was stirred at room

temperature for 48 hours, monitoring by TLC. After this time, water was added and the reaction mixture was extracted with chloroform. The organic layers were combined, dried with potassium carbonate and purified using flash column chromatography (ethyl acetate/hexane 1:1) to yield ABNO as a red solid in 29 % yield (0.434 g).

CHN analysis: calculated (found) C; 68.54% (68.08%), H; 9.99% (10.38%), N; 9.99% (9.85%).

HRMS (ESI⁺) Calc. for C₈H₁₅NO [M+H⁺] 140.1075, measured: 140.1075.

Synthesis of 9-azabicyclo[3.3.1]nonane-3-one *N*-oxyl (ketoABNO)

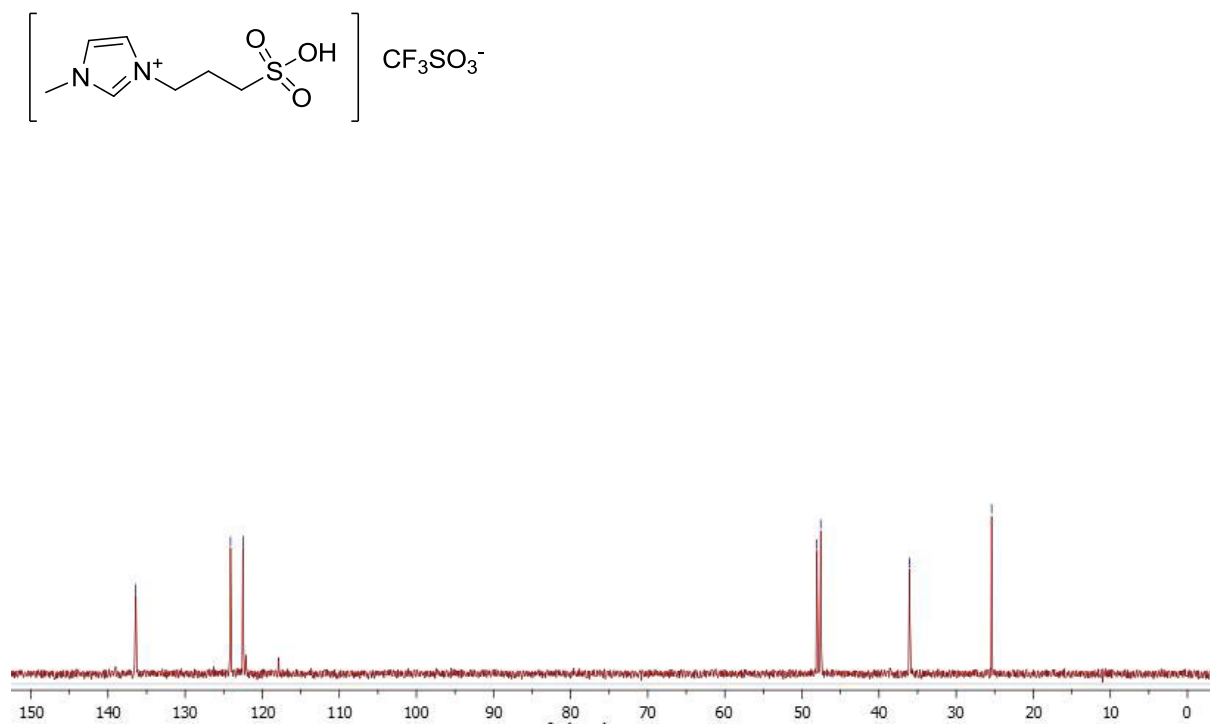
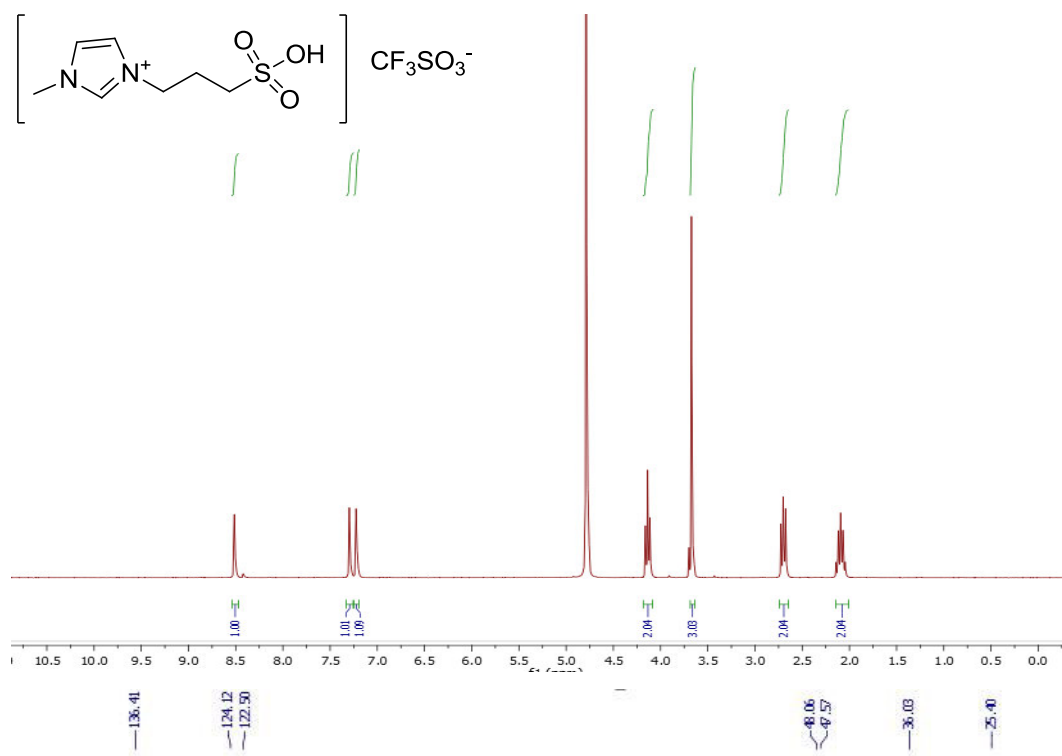


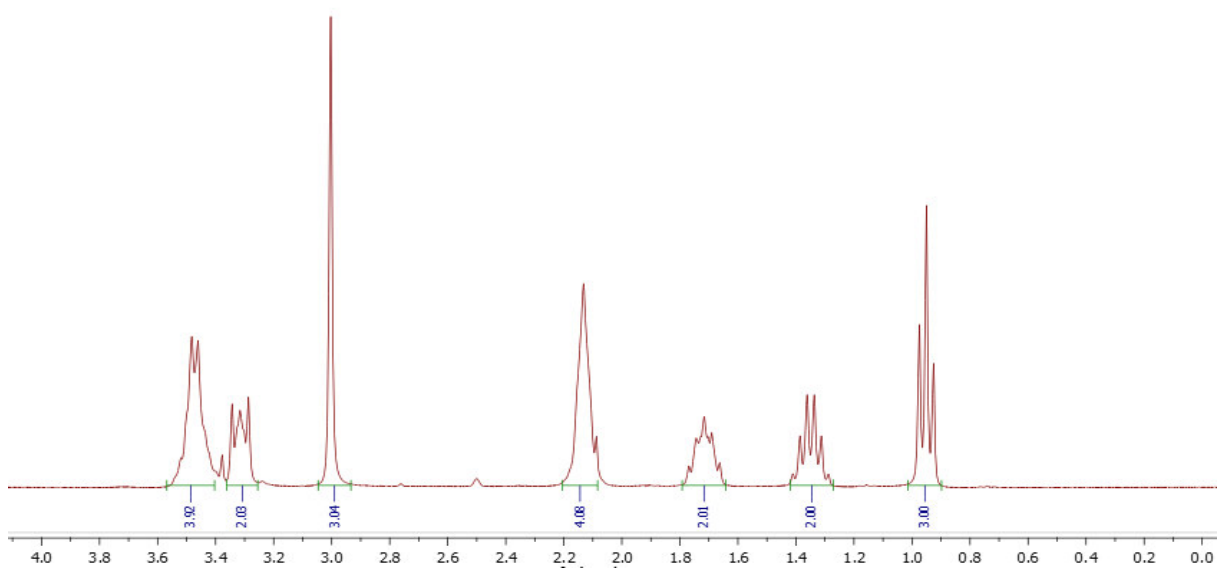
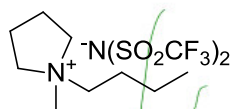
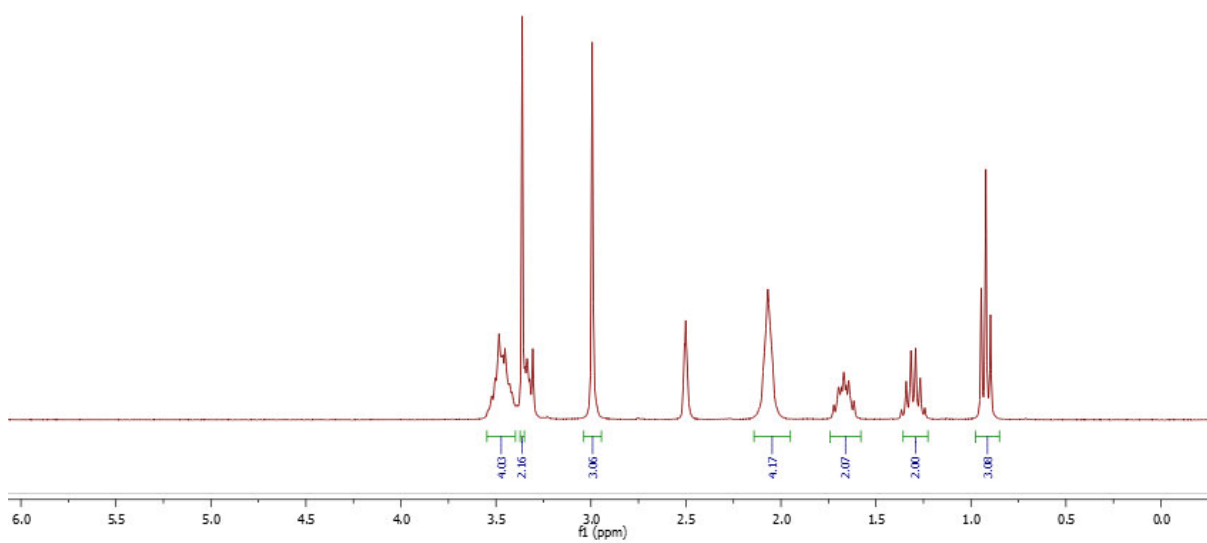
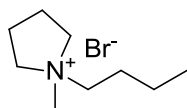
9-Azabicyclo[3.3.1]nonane-3-one *N*-oxyl was synthesised according to a literature procedure.³⁵ To a 250 mL round bottomed flask equipped with a stirrer bar was added 9-azabicyclo[3.3.1]nonane-3-one (3.05 g, 21.8 mmol) in 37 mL acetonitrile. Sodium tungstate dihydrate (0.72 g, 2.2 mmol) was added to the flask followed by slow addition of urea hydrogen peroxide (6.12 g, 65 mmol). The reaction mixture was stirred at room temperature for 48 hours, monitoring by TLC. After this time, water was added and the reaction mixture was extracted with chloroform. The organic layers were combined, dried with potassium carbonate and purified using flash column chromatography (ethyl acetate/hexane 1:1) to yield ketoABNO as a yellow solid in 47 % yield (1.6 g).

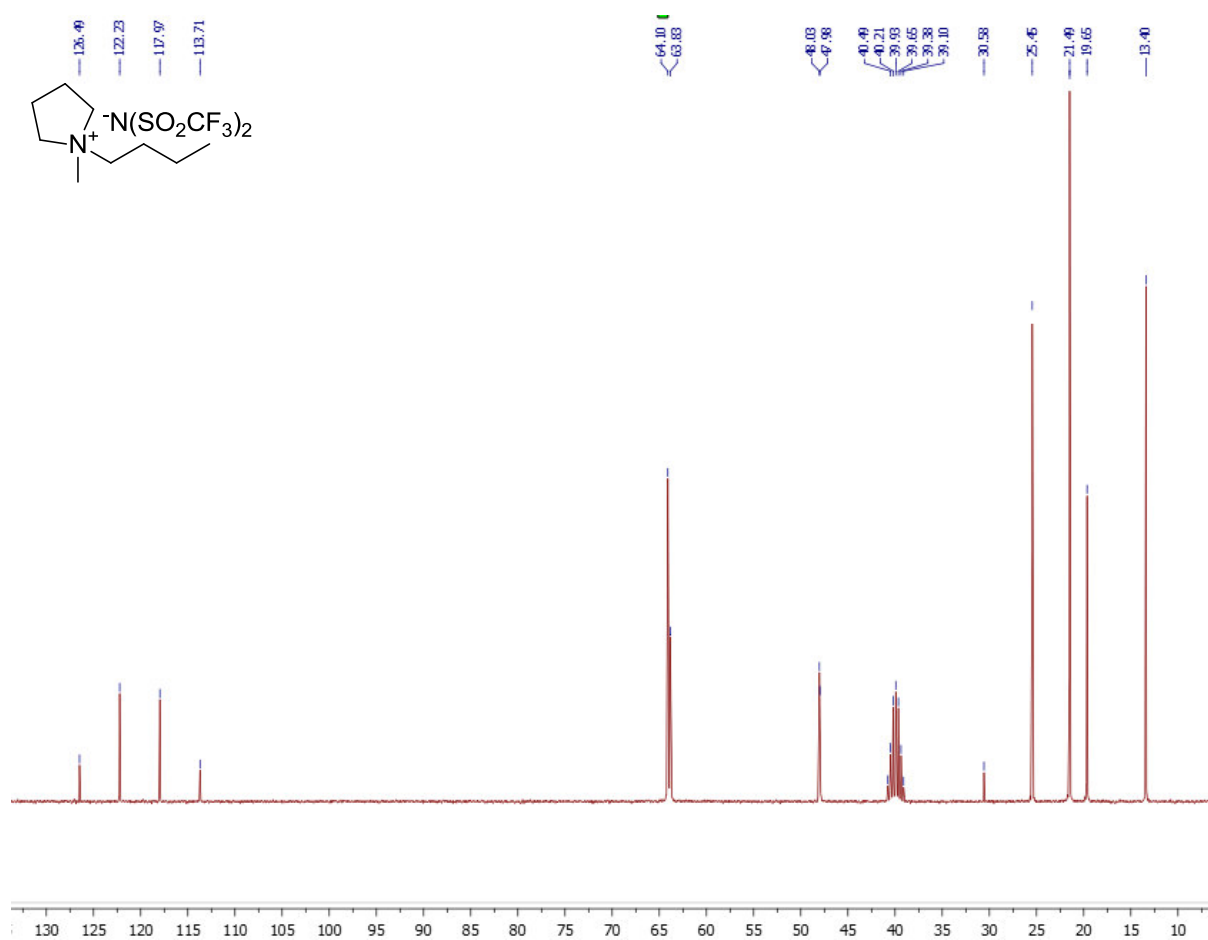
CHN analysis: calculated (found) C; 62.32% (62.62%), H; 7.84% (7.81%), N; 9.08% (8.77%).

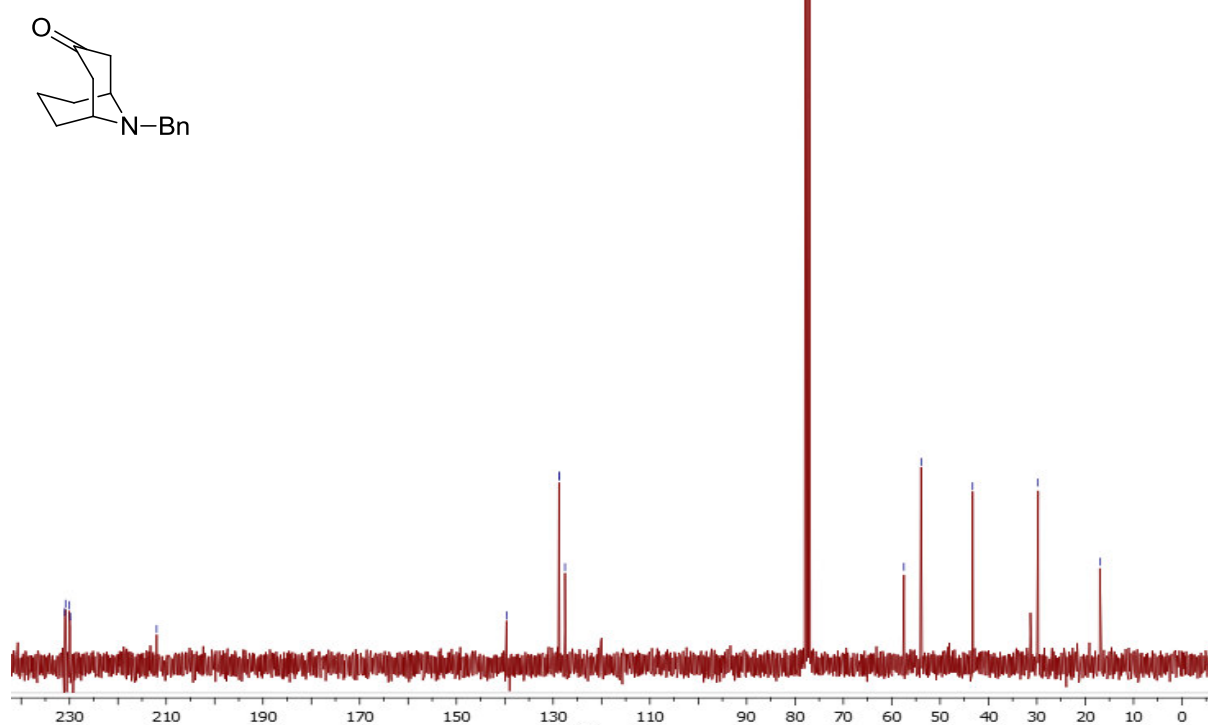
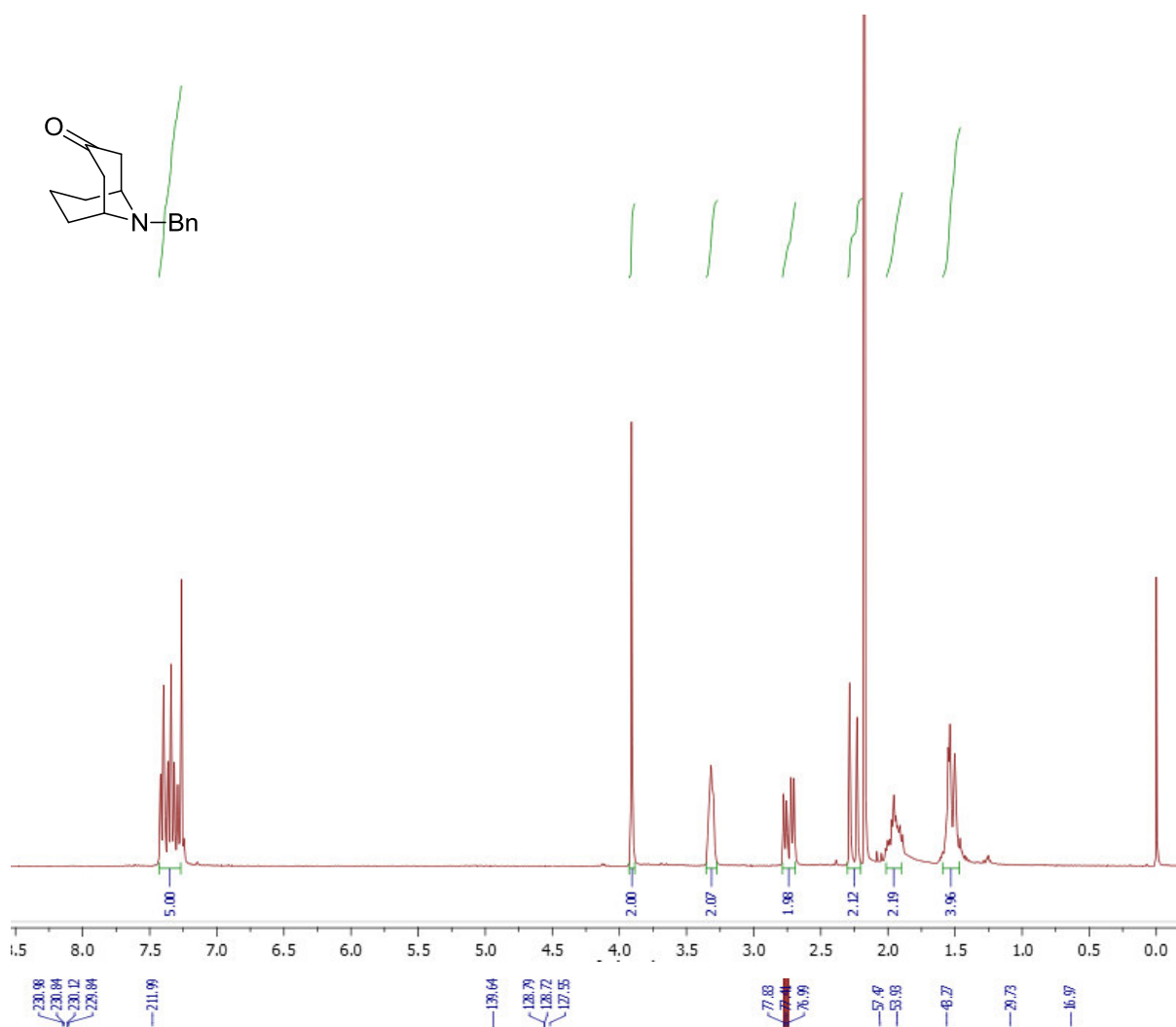
HRMS (ESI⁺) Calc. for C₈H₁₃NO₂ [M+H⁺] 154.09, measured: 154.0868.

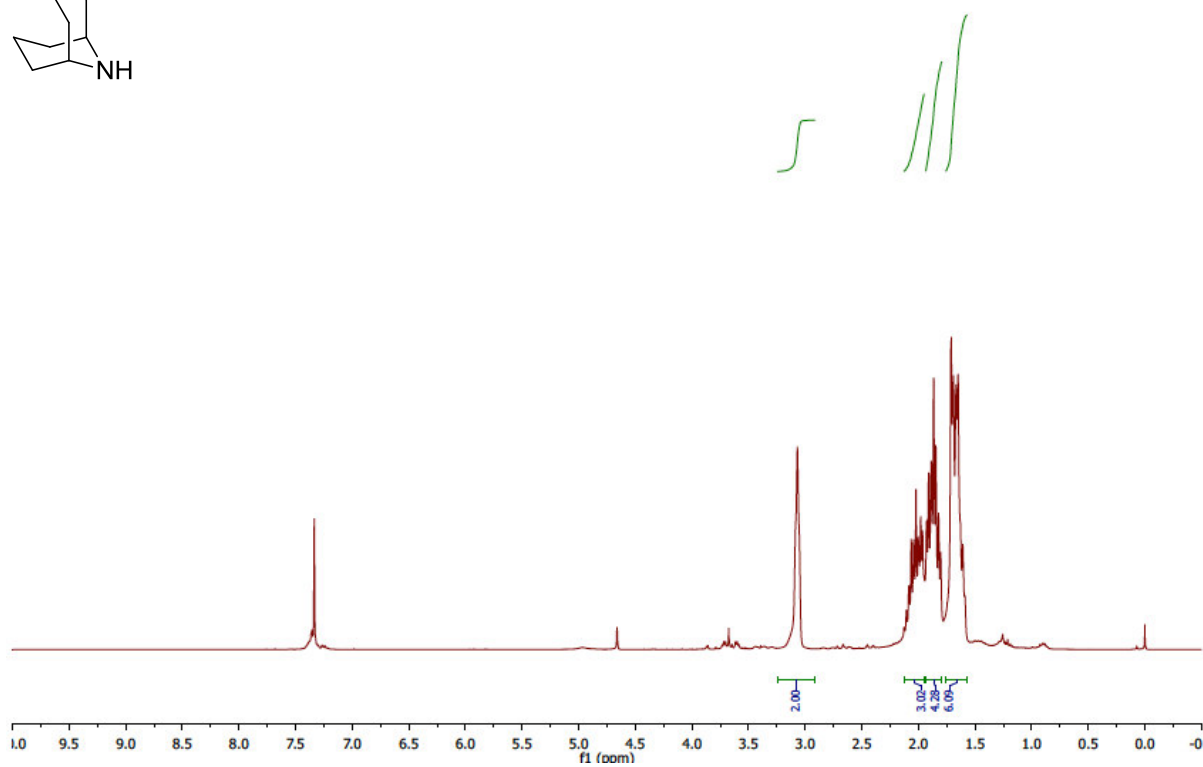
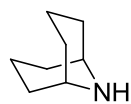
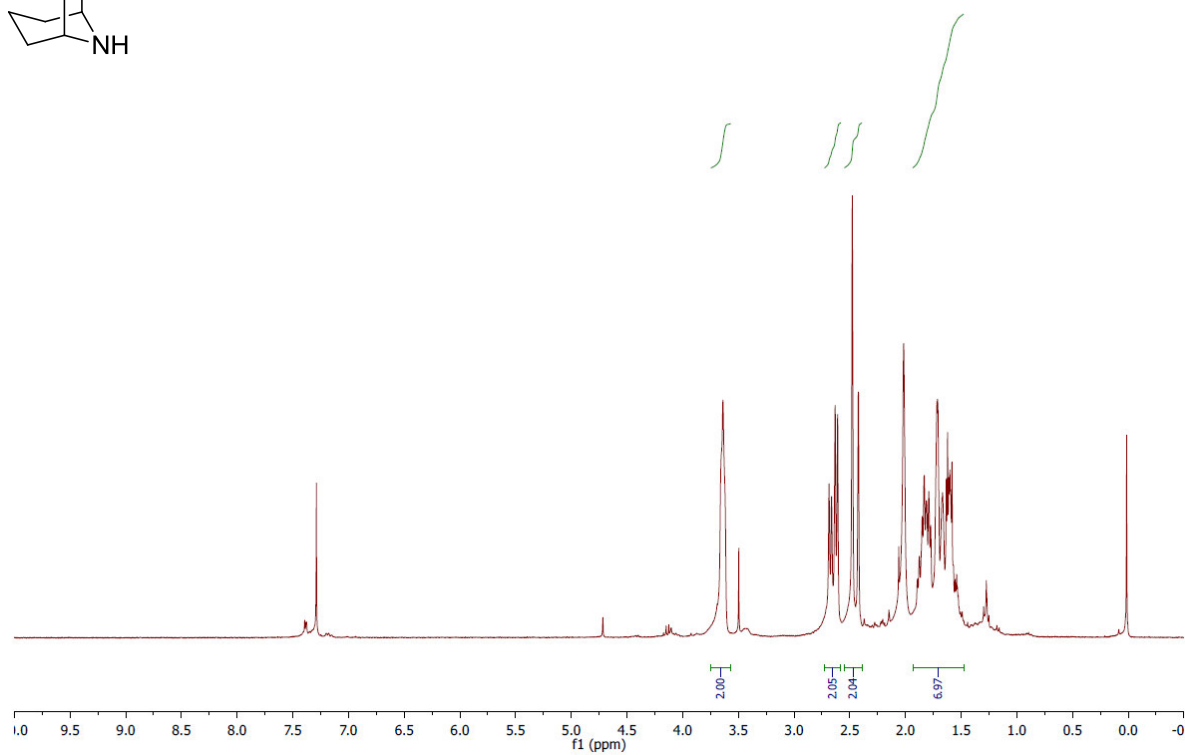
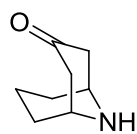
2.5.7 Spectra











2.6 References

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Chapter 3

Palladium(II) Catalysed Oxidative Carbonylation of Terminal Alkynes for the Synthesis of 2- Alkynoates

3.1 Introduction

3.1.1 Importance of 2-Alkynoate Synthesis

2- Alkynoates are an important class of compounds, proving highly useful as reaction intermediates in organic synthesis. For example, 2-alkynoates can undergo transformations to prepare a variety of heterocycles including, butenolides,¹ cyclopropanes,² furans,³ bicyclo[3.1.0]hexanes⁴ and bicyclo[3.2.0]hept-6-en-2-ones.⁵ Some examples of these transformations can be seen in Figure 3.1.

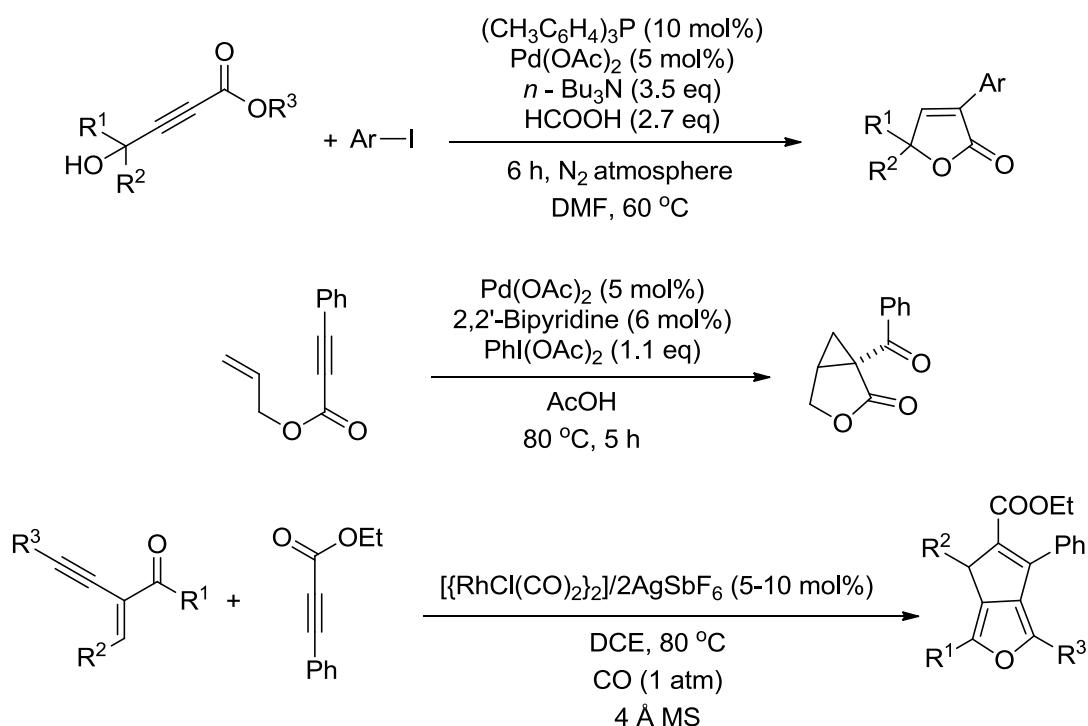


Figure 3.1 Synthesis of butenolides,¹ cyclopropanes² and furans³ via 2-alkynoates.

In addition, 2-alkynoates can be used in decarboxylative coupling reactions in combination with arynes to produce 1-allyl-2-ethynylbenzenes,⁶ or with allyl electrophiles to form 1,4-enynes.⁷ Electron deficient 2-alkynoates can also be reacted with phosphines to undergo transformations such as isomerisation,⁸ α -addition,⁹ γ -addition,¹⁰ and β -olefination.¹¹ These are summarised in Figure 3.2.

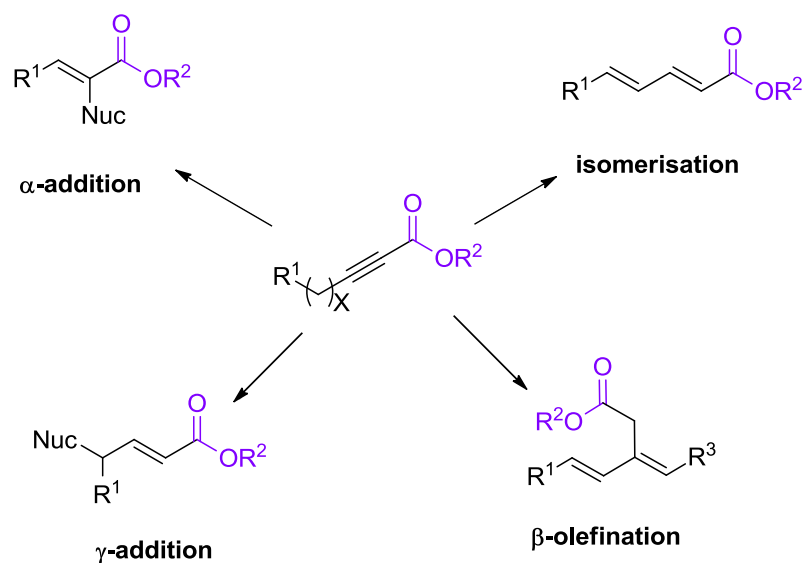


Figure 3.2 Potential transformations of 2-alkynoates under phosphine mediated conditions.¹¹

The importance of 2-alkynoates is further highlighted by their role in total synthesis of natural products. For example, ethyl phenylpropiolate is used in the total synthesis of (\pm) – celacinnine, (\pm) – celallocinnine, (\pm)– celafurine and (\pm)– celabenzine.¹² 2- Alkynoates are also present in biological molecules, for example in podophyllotoxin esters. In a series of derivatives, those containing the alkyne functionality demonstrated the highest cytotoxicity against lung, prostate, liver, breast and cervical cancers.¹³ The active podophyllotoxin is shown in Figure 3.3.

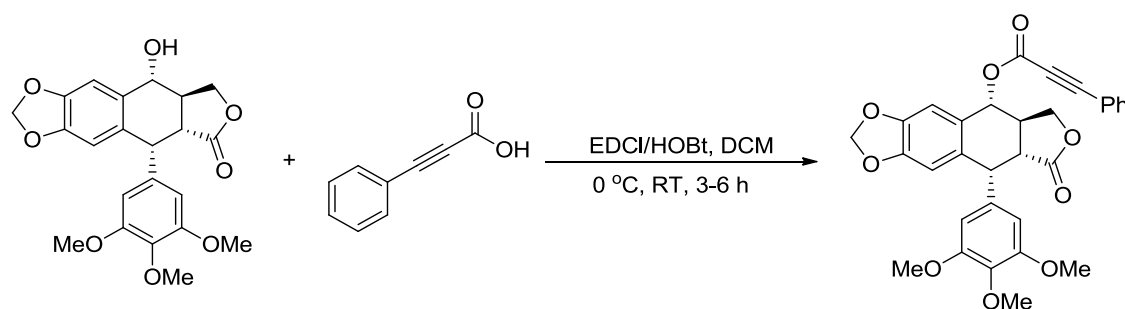
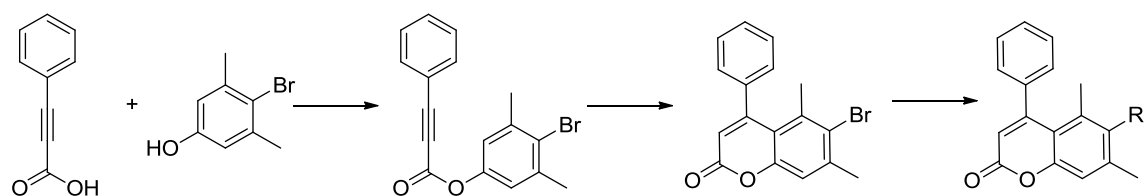
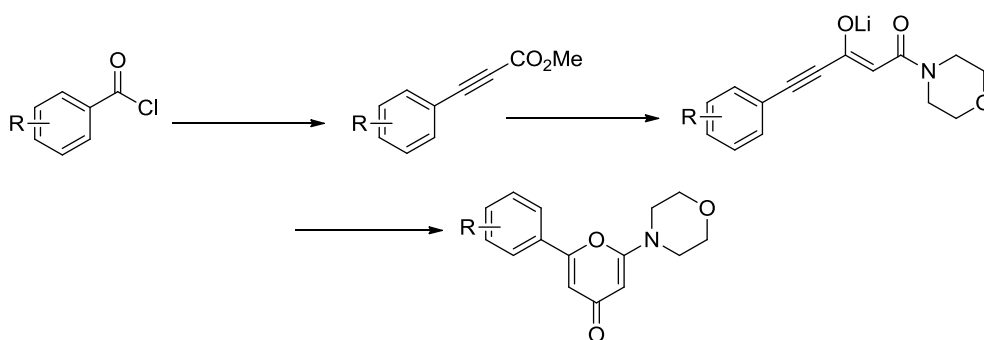


Figure 3.3 Synthesis of cytotoxic podophyllotoxin containing 2-alkynoate functionality.¹³

2-Alkynoates have been demonstrated to be key intermediates in the synthesis of phenyl substituted coumarins which have anti-tubercular activity,¹⁴ and DNA-PK (DNA- dependent protein kinase) inhibitors, which can be used in radio and chemotherapy to target cancer cells.¹⁵ The synthesis of these are outlined in Figure 3.4.



Synthesis of phenyl substituted coumarins



Synthesis of DNA-PK inhibitors

Figure 3.4 Synthesis of biological molecules *via* 2-alkynoates.^{14,15}

3.1.2 Traditional Synthesis of 2-Alkynoates

Many synthetic methods currently exist for the synthesis of 2-alkynoates. The first of these involves the deprotonation of a terminal alkyne, by a strong base such as *n*-butyllithium (*n*-BuLi)¹⁶ or lithium diisopropylamide (LDA).¹⁷ The resulting alkyl lithium is then trapped with an appropriate chloroformate to yield the desired carbonyl product. Alternatively, a Grignard reagent such as ethyl magnesium bromide can be used, followed by the aforementioned chloroformate step.¹⁸ (Figure 3.5)

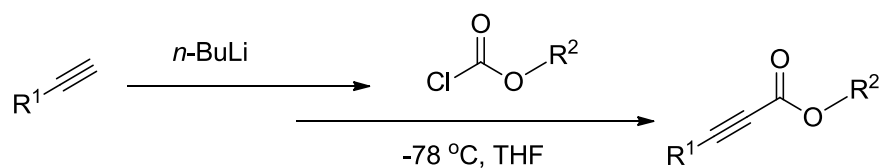


Figure 3.5 Synthesis of 2-alkynoates *via* lithiation.¹⁶

Alternatively, 2-alkynoates can be synthesised from an aldehyde, in a modified Corey Fuchs protocol. This method was demonstrated by Miesch and co-workers in an attempt to synthesise hydroxyl esters in a diastereoselective manner.¹⁹ The first step in the reaction is analogous to the traditional Corey Fuchs transformation, whereby the bromoolefin is prepared from the aldehyde and tetrabromomethane. However, the bromoolefin is then reacted with the appropriate chloroformate and *n*-BuLi, instead of the traditional hydrolysis to form an acetylene. The synthetic route can be seen in Figure 3.6 below.

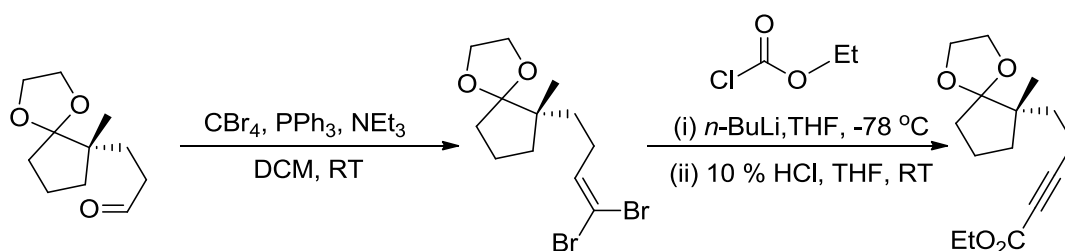


Figure 3.6 Synthesis of 2-alkynoates *via* an alternative Corey Fuchs protocol.¹⁹

It is also possible to carry out the esterification of alkynyl carboxylic acids with coupling reagents such as *N,N'*-dicyclohexylcarbodiimide (DCC)^{14,20} or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and hydroxybenzotriazole (HOBt).¹³ (Figure 3.7)

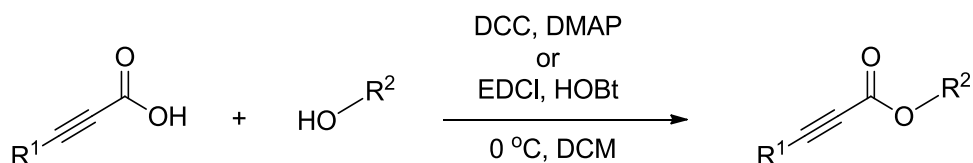


Figure 3.7 Synthesis of 2-alkynoates *via* esterification.^{13,14,20}

These methods offer a significant number of drawbacks. They require stoichiometric amounts of hazardous reagents such as *n*-BuLi and carbodiimide coupling reagents. Not only is the use of these reagents potentially harmful to the user, but the strength of base such as in the case of *n*-BuLi or LDA results in substrate scope limitations, as base sensitive substrates cannot be used. In addition, the alkynyl carboxylic acids are not widely commercially available, and so must be synthesised before use.

3.1.3 Catalytic Carboxylative Coupling with CO₂ for the Synthesis of 2-Alkynoates

2-Alkynoates can be synthesised by the catalytic carboxylative coupling of terminal alkynes with alkyl halides and CO₂.²¹ This is a highly desirable synthetic route as the use of a catalytic method is undoubtedly preferable to the previously reported stoichiometric synthesis. In addition, CO₂ is an abundant, inexpensive source of C₁. The first example of catalytic preparation of 2-alkynoates *via* carboxylative coupling was proposed by Inoue and co-workers in 1994.²² They demonstrated a reaction system that allowed for the direct coupling of terminal alkynes with CO₂ and bromoalkanes, utilising a Cu(I) or Ag(I) catalyst. (Figure 3.8)

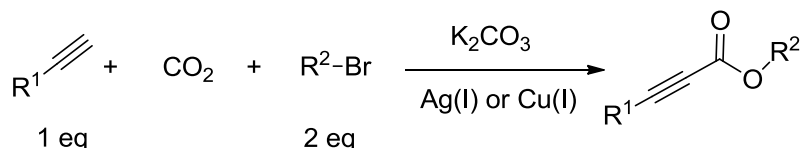


Figure 3.8 First example of carboxylative coupling.²²

During the reaction optimisation they found that the choice of solvent and base were crucial to the success of the reaction system. Only polar aprotic solvents such as DMF (dimethylformamide) and *N*-methylpyrrolidone gave the desired product. With regards to the base, triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in alkylation of the base by the bromoalkane. Weaker inorganic bases such as potassium phosphate and potassium carbonate yielded the 2-alkynoate product. The optimised reaction conditions worked well with aliphatic and aromatic alkynes, however problems occurred with attempts to use functionalised alkynes. Substituents including, ethyl, butyl and hydroxyl were either unsuccessful or very slow.

In 2010, Zhang and co-workers overcame this problem through the use of less reactive allylic and benzylic chlorides, in combination with an *N*-heterocyclic carbene Cu(I) catalyst.²³ The system had similarities with that of Innoue and co-workers²² as it utilised potassium carbonate as the base, in DMF. Their optimised reaction system (Figure 3.9) could be used for a variety of aromatic functionalised alkynes with both electron donating and electron withdrawing substituents. The system was slower with aliphatic alkynes, and gave a reduced yield when using substrates containing nitrogen atoms. A major advantage of their system was the ability to recover up to 94% of the *N*-heterocyclic carbene Cu(I) catalyst by column chromatography after the reaction.

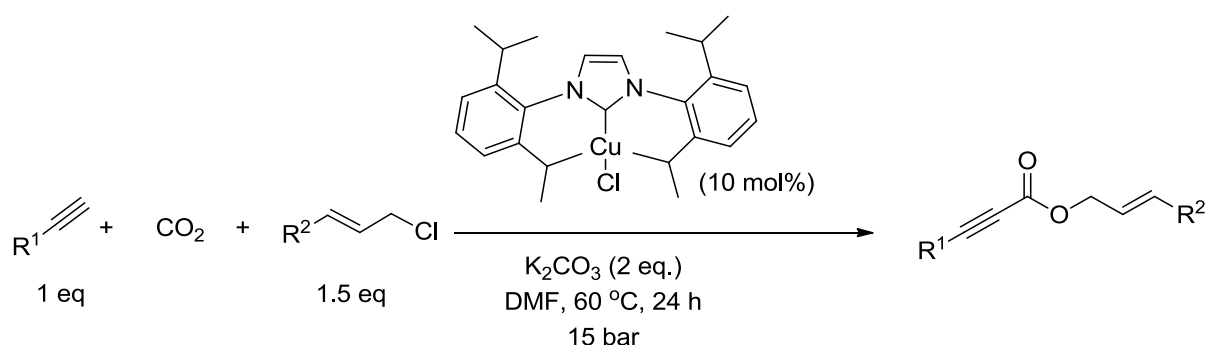
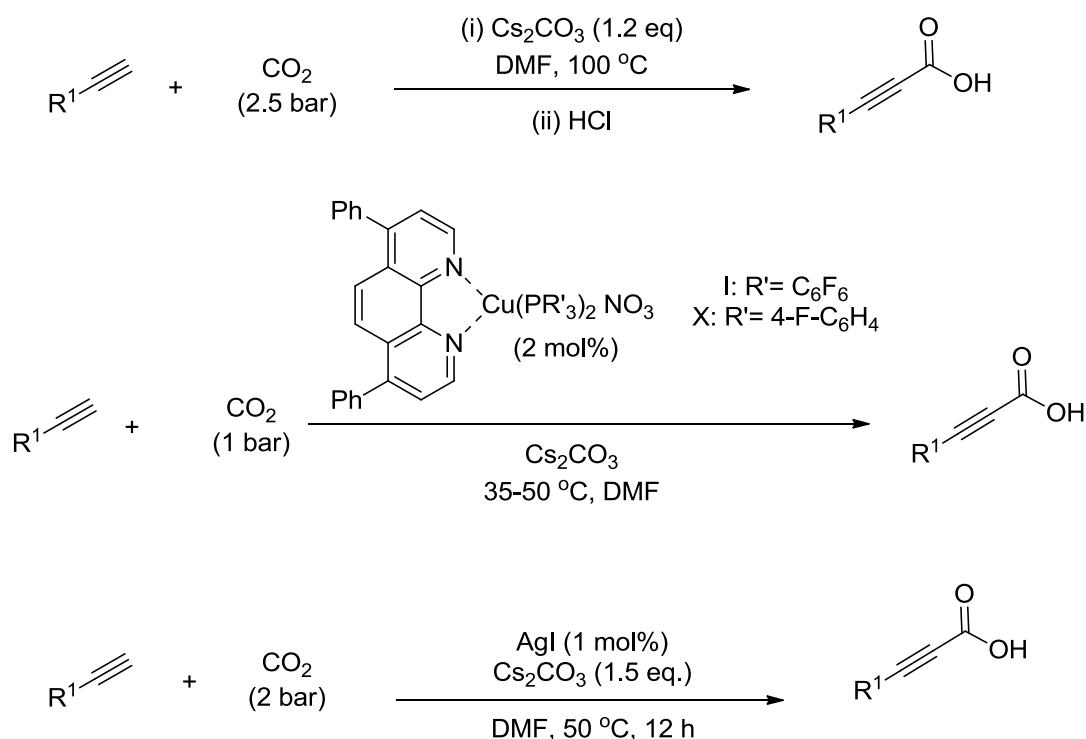


Figure 3.9 Carboxylative coupling of allylic chlorides and terminal alkynes.²³

Dingyi and Yugen later reported the use of a copper- NHC system for the synthesis of propiolic acids.²⁴ In a follow up paper, they reported a ligand free

system for the synthesis of propiolic acids which proceeds *via* the 2-alkynoate. The reaction is performed, and then followed by an acid hydrolysis with hydrochloric acid.²⁵ Similar systems were proposed by Gooßen²⁶ and Zhang.²⁷ A summary of these catalytic systems can be seen in Figure 3.10. These systems, despite being utilised for the synthesis of propiolic acids, still have similarities with the systems presented for the synthesis of 2-alkynoates. For example, the reactions use Cu(I) or Ag(I) catalysts, require polar aprotic solvents such as DMF and carbonate bases are superior.



3.10 Examples of carboxylative coupling for the synthesis of propiolic acids.^{25,26,27}

Inspired by their work on propiolic acids²⁷ Zhang and co-workers reported another system that only required 0.1 mol% AgI for the synthesis of 2-alkynoates.²⁸ This method demonstrated an activity 300 times greater than the previously reported copper-NHC system.²³ Once again, it was run in DMF, at 60 °C, however this time the system could be applied to a more diverse range of allylic, propargylic and benzylic chlorides.

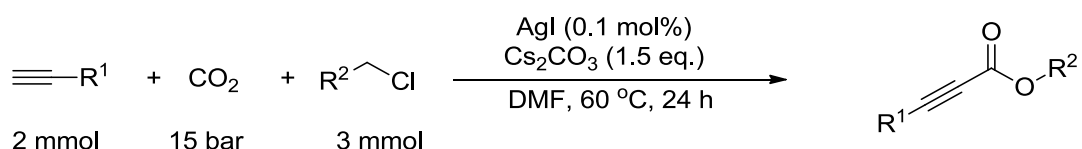


Figure 3.11 Zhang carboxylative coupling using 0.1 mol% AgI.²⁸

Later the same year, Inamoto and co-workers reported a method that utilised copper(I) iodide with triethylphosphine and caesium carbonate in DMA.²⁹ The reaction could be run at room temperature, with 1 atm CO₂. The optimised reaction conditions can be seen in Figure 3.12.

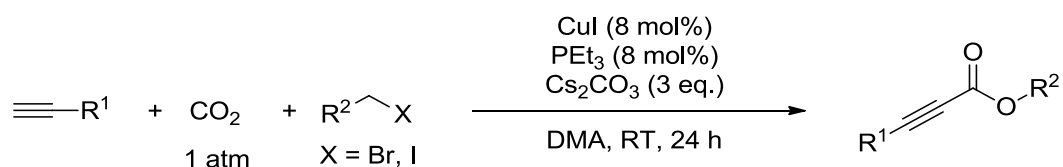


Figure 3.12 Inamoto and co-workers copper catalysed carboxylation for the synthesis of 2-alkynoates.²⁹

They reported that the ligand choice was crucial with selected substrates. For example, when using phenylacetylenes with electron donating groups, PEt₃ gave the best performance.²⁹ However in the case of phenylacetylenes with electron withdrawing groups, 2,2'-bipyridine was superior. The authors didn't offer an explanation as to why this may be the case. With regard to heteroatoms, 3-ethynylthiophene gave a high yield, yet 2-ethynylpyridine was remarkably slow, resulting in only a trace of desired product. Perhaps this may be due to the ability of 2-ethynylpyridine to chelate with the copper catalyst, resulting in deactivation of the catalyst. A variety of alkyl halides were also tested, with alkyl iodides and bromides performing well, in contrast to alkyl chloride and triflate which showed no activity. Again, caesium carbonate was found to deliver the highest performance as a base. When the system was doped with additional equivalents of water, the system shut down completely.

This suggests an explanation as to why a relatively hygroscopic base is required to remove any water during the reaction.²⁹

Wang and co-workers also reported a method utilising copper(I) iodide, in the presence of caesium carbonate.³⁰ In this case, the reaction solvent was ethylene carbonate, considered to be a more desirable solvent than those previously reported. The optimised system was tested on a variety of substituted alkynes, to give yields competitive with those reactions reported in more conventional solvents.

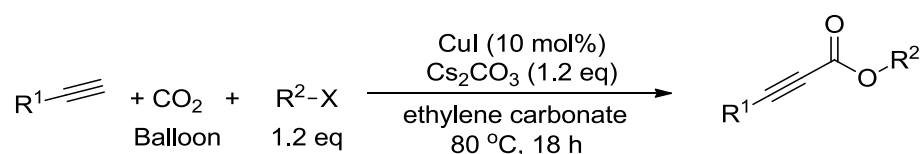


Figure 3.13 Cu(I) catalysed carboxylation in ethylene carbonate.³⁰

These methods, despite being catalytic still have several drawbacks. Firstly, they require the use of alkyl halides, which limits the substrate scope of the reaction as these are not as widely commercially available as other potential starting materials. In addition, the reaction only proceeds in the presence of an excess of inorganic base and is not applicable for use with secondary substrates. It would be preferable if the reaction could be performed *via* an alternative catalytic route.

3.1.4 Palladium(II) Catalysed Oxidative Carbonylation for the Synthesis of 2-Alkynoates

A desirable alternative to carboxylation, is to carry out Pd(II) catalysed oxidative carbonylation of terminal alkynes with alcohols and carbon monoxide. Palladium carbonylations have been widely studied,³¹ however oxidative carbonylations are less established than other Pd(II) catalysed oxidations, such as alcohol oxidation.³² Palladium catalysed oxidative carbonylations work similarly to other palladium(II) catalysed reactions, whereby the palladium(II) is firstly reduced, allowing a reaction to occur between the substrates (alkyne, alcohol and CO gas) to form the desired 2-alkynoate. The palladium(0) must then be reoxidised by a terminal oxidant

to complete the catalytic cycle. In an ideal world, this terminal oxidant would be molecular oxygen or air, as it is cheap, non-toxic and its sole by-product is water. However, palladium(0) is known to aggregate in a competing reaction to form palladium black, resulting in catalyst death. This reaction competes with the reoxidation, and so it may sometimes be necessary to have an additional co-catalyst or electron transfer mediator (ETM) in order to bridge the energy gap of the electron transfer. For example, an electron transfer mediator can allow for the electrons to be transferred from the metal to the oxidant *via* a lower energy pathway.³³ The general reaction cycle can be seen in Figure 3.14.

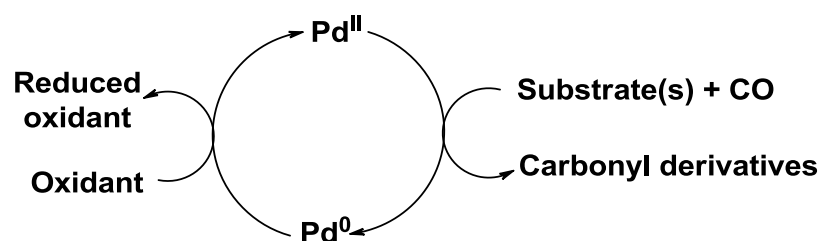


Figure 3.14 Cascade reaction cycle for palladium(II) catalysed oxidations.³³

Oxidative carbonylation has the potential to be a powerful tool in organic synthesis, as CO is a cheap, inexpensive way of introducing a carbonyl group into a molecule. In addition, if it were possible to apply molecular oxygen or air as the terminal oxidant it would be a more sustainable method of synthesising 2-alkynoates.

The first example of oxidative carbonylation was demonstrated by Tsuji and co-workers in 1980.³⁴ They reported a system that used palladium and copper chlorides in combination with sodium acetate to afford 2-alkynoates in fair to good yields. In this case, copper chloride was used stoichiometrically to reoxidise the Pd(0). Benzoquinone was also tested for this purpose, however the reaction took five times as long to achieve the same yield as when employing copper chloride.

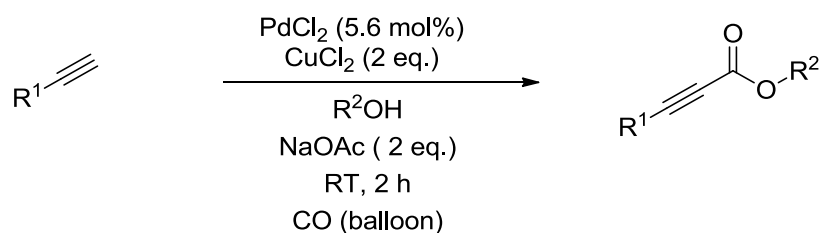


Figure 3.15 First example of Pd(II) oxidative carbonylation.³⁴

This system opened up the possibility of oxidative carbonylations for 2-alkynoate synthesis, however the use of stoichiometric $CuCl_2$ and excess alcohol, make this method less desirable. Chen and co-workers reported a similar system, utilising $PdBr_2$ and $CuBr_2$ in excess alcohol to afford 2-alkynoates.³⁵ Several bases were tested, with $NaHCO_3$ giving the best result, however interestingly when *n*-butanol or isopropyl alcohol were used in replacement of methanol, it was necessary to employ sodium acetate as the base.

In 1999, Ishii and co-workers reported the use of molybdovanadophosphate (NPMoV), a polyoxometalate as an electron transfer mediator (ETM), to aid the reoxidation of palladium(0) by molecular oxygen.³⁶ (Figure 3.16)

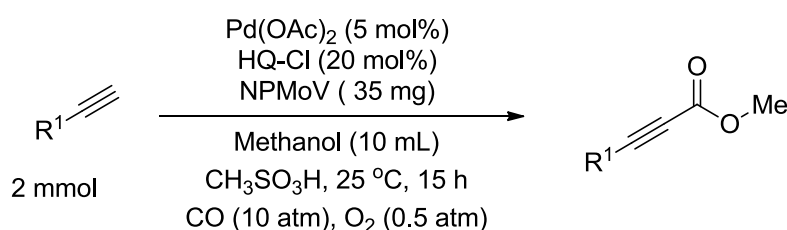
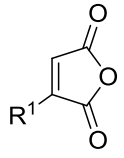
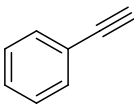
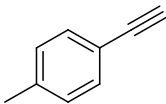
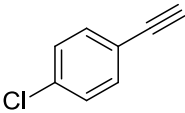
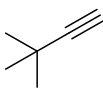
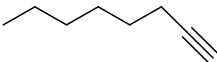
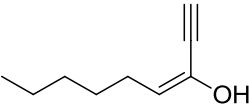


Figure 3.16 Use of NPMov as an ETM in oxidative carbonylation.³⁶

This method did not require the use of a stoichiometric co-catalyst such as copper(II) chloride, as the palladium(0) could be reoxidised smoothly through the use of the three cascade catalytic system (POM, HQ-Cl and Pd(II)). The reaction was run under a CO rich atmosphere of CO/ O_2 (10/0.5 atm) in an

excess of methanol. It was also reported that if the reaction solvent, methanol, was exchanged for 1,4-dioxane, an alternate product, the maleic anhydride was formed. The results of the substrate scope in both solvents can be seen in Figure 3.17.

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center; margin-right: 20px;"> $R^1\text{C}\equiv\text{C}$ 2 mmol </div> <div style="text-align: center; margin-right: 20px;"> <math>\xrightarrow[\text{CH}_3\text{SO}_3\text{H}, 25\text{ }^\circ\text{C}, 15\text{ h}]{\text{Pd}(\text{OAc})_2\text{ (5 mol\%)} \text{HQ-Cl (20 mol\%)} \text{NPMoV (35 mg)}}\text{CO/ O}_2</math> </div> <div style="display: flex; flex-direction: column; align-items: center;"> <div style="margin-bottom: 10px;"> $\xrightarrow{\text{Methanol (10 mL)}}$ </div> <div style="margin-bottom: 10px;"> $\xrightarrow{\text{1,4-Dioxane (10 mL)}}$ </div> </div> <div style="display: flex; flex-direction: column; align-items: center;"> <div style="margin-bottom: 20px;"> $R^1\text{C}\equiv\text{C}-\text{C}(=\text{O})\text{OMe}$ </div> <div>  </div> </div> </div>		
Substrate	Yield in Methanol [%] ^a	Yield in 1,4- Dioxane [%] ^b
	85	62
	61	63
	62	36
	70	13
	63	18
	Mixture	36

a. Under CO/ O₂ (10/0.5 atm)
b. Under CO/O₂ (20/1 atm)

Figure 3.17 Carbonylation of alkynes utilising polyoxometalates.³⁶

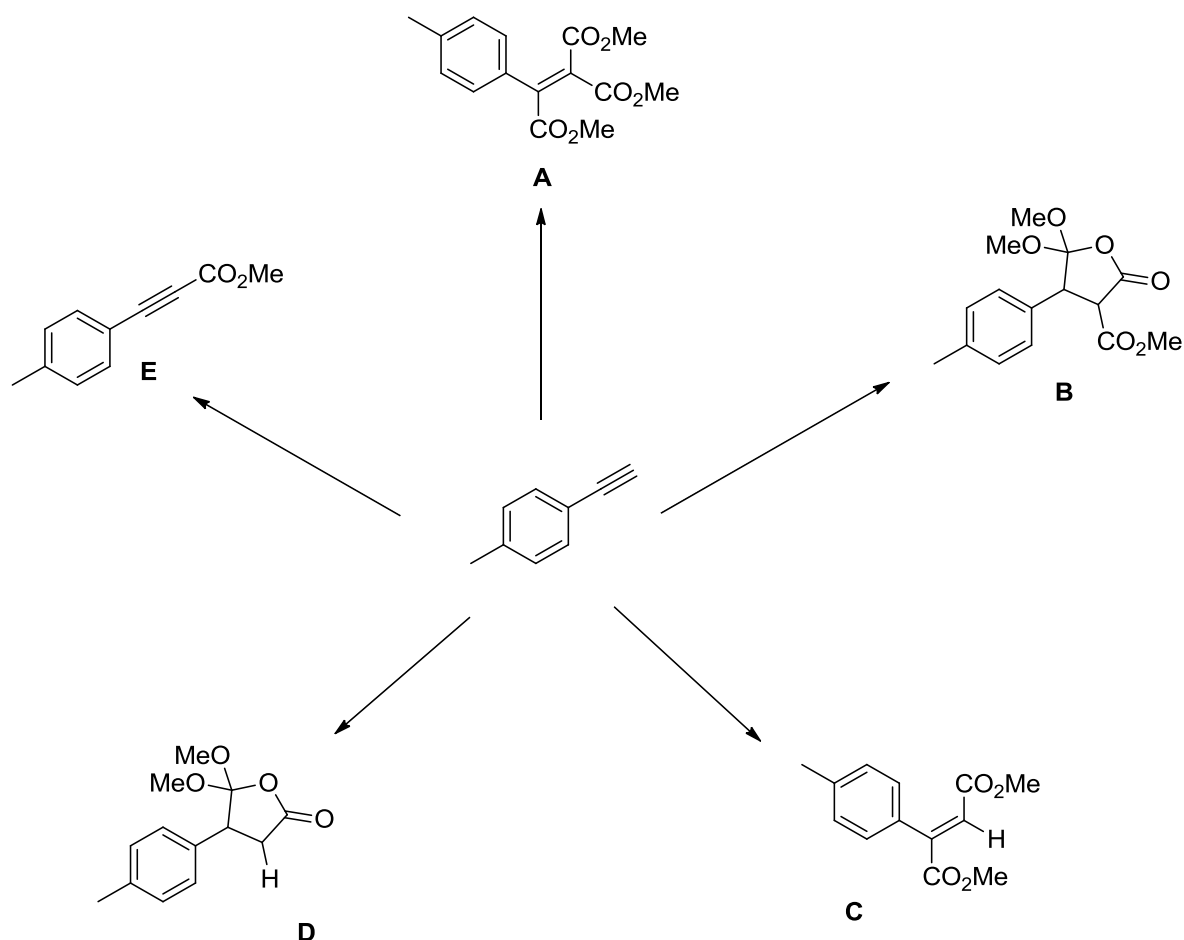
This method despite demonstrating oxygen as the terminal oxidant still has several drawbacks. The use of the alcohol substrate as a solvent greatly limits

the substrate scope of the reaction, whereas this is not problematic with simple alcohols such as methanol, more complex alcohols are too expensive to use in such large quantities. Use of the alcohol as a solvent, is also more difficult in cases where the alcohol is a solid. In addition, the complex mixtures obtained when using (*E*)-non-3-en-1-yn-3-ol as the substrate, is a key demonstration of the poor selectivity of the reaction. At first glance, the ability to change the product on varying the solvent to 1,4-dioxane may seem advantageous, however the yields obtained are in general poor.

A later paper by Yamamoto and co-workers also demonstrated that a change in solvent could result in a range of products.³⁷ This reaction also used $\text{Pd}(\text{OAc})_2$, however in this case, a triphenylphosphine ligand was employed. Ligands can also be used to stabilise $\text{Pd}(0)$ and so prevent the need for an electron transfer mediator.³³ It was highlighted that in the presence of iodide additives, such as sodium iodide or tetraethylammonium iodide $[\text{NEt}_4][\text{I}]$, it was possible for di- and tricarbonylation to occur. The possible products under these reaction conditions can be observed in Figure 3.18.

It was reported that when running the reaction in a 5:1 mixture of THF: Methanol, the sole product was the monocarbonylation 2-alkynoate product (Figure 3.18, E). When THF was replaced with DMF in either 5:1 or 1:1 ratios, the tricarbonylation products (Figure 3.18, A and B) were formed. However, if the ratio was reversed to give a methanol concentrated mixture, then this resulted in an increase of the dicarbonylation products (Figure 3.18, C and D). Interestingly, when only methanol was used as the reaction solvent, all products except the 2-alkynoate product were observed. It was also noted that only the monocarbonylation product was formed in the absence of the iodide additive. This demonstrates the complexity of the reaction mechanism, in that only small changes in solvent concentration can have such a large effect on the product obtained. This is a disadvantage of the reaction method, as the selectivity towards a single product is poor, with the highest yield obtained being only 66%. In addition, the use of THF as a solvent is ill-advised under oxidative conditions due to its propensity to form peroxide species. In fact, these peroxides are so readily formed that they have been shown to be a key catalytic component in various oxidative reactions.³⁸ This means that not only

does the use of THF increase the risk of the reaction, but also is a hazard when being stored in the lab for long periods of time.



Reaction Conditions: 4-ethynyltoluene (1 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol%), PPH_3 (20 mol%), NaI (0.5 eq.) solvent (10 mL), 60 °C, 24 h, CO (15 atm), O_2 (5 atm).

Figure 3.18 Potential mono-, di-, and tricarbonylation products under Yamamoto reaction conditions.³⁷

Yamamoto and co-workers also developed a more selective method for the oxidative carbonylation of 2-alkynoates and carried out preliminary mechanistic studies on the reaction system.³⁹ As previously mentioned, their group were the first to employ ligands to improve palladium stability. They tested a variety of phosphine ligands including triphenylphosphine, 1,4-bis(diphenylphosphino)butane (dppb), and sterically hindered ligands such as tri-*tert*-butyl phosphine and tri-*o*-tolylphosphine. Triphenylphosphine gave the best results, as strongly co-ordinating bidentate ligands proved unsuitable for the reaction, and bulky ligands were observed to shut the reaction down. It was found that $\text{Pd}(\text{OAc})_2$ and triphenylphosphine gave a substantive yield of 83%,

however when using PdCl₂ and triphenylphosphine, it was necessary to add sodium acetate to achieve the same yield. This would suggest that acetate is a key component in the reaction system. The optimised reaction conditions can be seen in Figure 3.19 alongside the reported substrate scope.

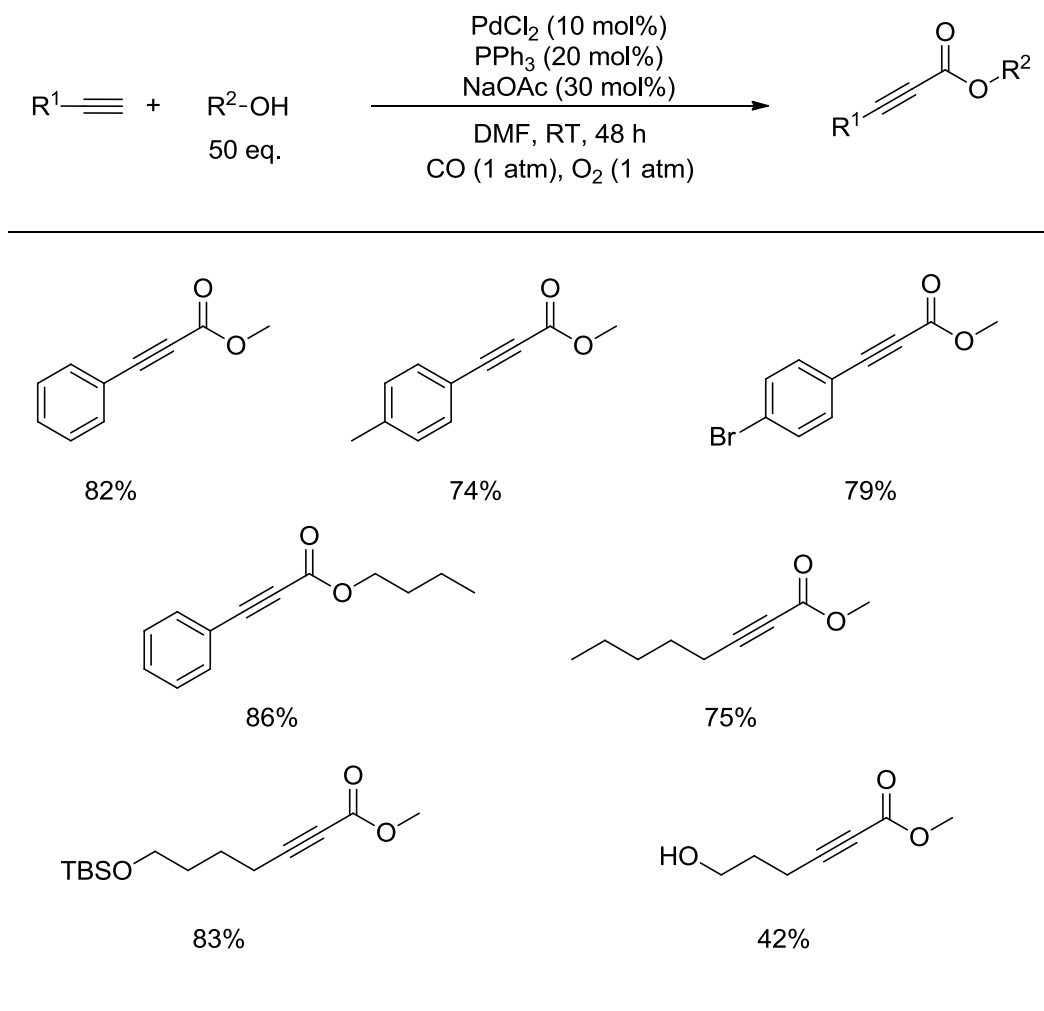


Figure 3.19 Oxidative carbonylation utilising triphenylphosphine ligand.³⁹

The reaction proceeded well with both aromatic and aliphatic alkynes. In the case of substituted aryl alkynes, both electron withdrawing and electron donating groups could be tolerated. Unfortunately when a hydroxyl group was present on the alkyne, a poor yield was obtained. To solve this, the authors tested the hydroxyl-protecting group, *tert*-butyldimethylsilyl (TBSO), to find the reaction could proceed smoothly. It was also possible to use *n*-butanol to achieve the same high yields, however *tert*-butyl alcohol showed no reaction.³⁹

The authors then examined the reaction mechanism by firstly proposing three possible mechanistic routes, and then synthesising key intermediates within these routes to test their viability. The resulting suggested mechanism can be seen in Figure 3.20.

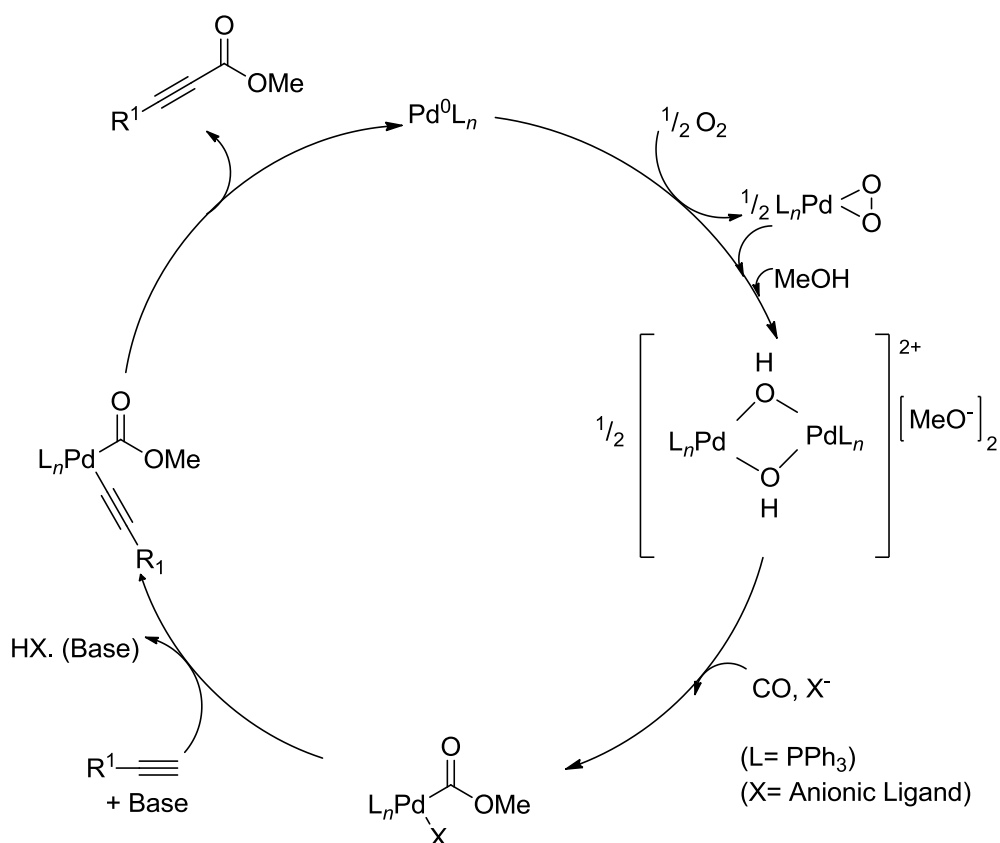


Figure 3.20 Proposed mechanism for oxidative carbonylation of alkynes with CO and methanol using oxygen as the terminal oxidant.³⁹

It is proposed that the first step in the reaction mechanism is the formation of a bridged dimeric species composed of hydroxide anions, formed by a reaction between the palladium(II) complex and methanol. Carbon monoxide is then inserted into the Pd-O bond, resulting in the formation of a methoxycarbonyl palladium intermediate, into which the alkyne is inserted in the presence of a base. The resulting alkynylpalladium species can undergo reductive elimination to form the desired carbonyl product, carbon monoxide and Pd(0). The Pd(0) is then reoxidised by molecular oxygen to complete the catalytic cycle.

This paper is an excellent example of utilising ligands for oxidative carbonylations to improve the stability of the palladium. This avoids the use of additional electron transfer mediators, or stoichiometric co-catalysts such as CuCl_2 which may cause chlorinated byproducts, resulting in a problematic product isolation. In addition, the use of ligands introduces the potential to tune and improve the catalyst either electronically, sterically, or both. However, the use of phosphine ligands under oxidative conditions is not ideal, as these can be readily oxidised resulting in loss of the ligand. It would be preferable to use non-oxidising ligands such as nitrogen donating ligands.

The authors suggested the idea of using Pd/C as a heterogeneous catalyst for oxidative carbonylation. It is probable that in this case the reaction proceeds *via* a different mechanism as the reaction commences with Pd(0). When this was tested they found that in order to achieve a high yield, it was necessary to use a higher pressure of 50 atm CO and 7.5 atm O_2 .³⁹ Despite the high pressures required, the use of a heterogeneous system holds advantages over a homogeneous system, such as ease of catalyst separation at the end of the reaction, and the potential for catalyst recycling. In 2013 Gadge and Bhanage reported a heterogeneous method for the oxidative carbonylation of alkynes and alcohols utilising Pd/C in combination with tetrabutylammonium iodide, $[\text{NBu}_4][\text{I}]$.⁴⁰ They performed an extensive reaction optimisation, testing various reaction parameters including solvent, additive, temperature and reaction time. They found that non-polar solvents performed poorly, with 1,4-dioxane achieving the best results. Several additives were tested such as KI, KBr, tetrabutylammonium bromide $[\text{NBu}_4][\text{Br}]$ and tetrabutylammonium iodide $[\text{NBu}_4][\text{I}]$. It was found that $[\text{NBu}_4][\text{I}]$ gave the best results. It was postulated that $[\text{NBu}_4][\text{I}]$ outperformed $[\text{NBu}_4][\text{Br}]$ due to the 'softer' binding ability of iodide, when compared to bromide. It may also be that the tetrabutylammonium cation aids solubility in the reaction solvent. The preferred reaction temperature was found to be 80 °C, with a reaction time of eight hours.

The optimised reactions conditions were then applied to a variety of aliphatic and aromatic alkynes. It was found that aromatic alkynes were higher in reactivity than their aliphatic counterparts. In the case of substituted aryl

alkynes, little difference was observed when using electron donating or electron withdrawing groups. A small selection of primary alcohols were also tested, although again these showed only small variations in performance.⁴⁰ A selection from the substrate scope can be seen in Figure 3.21.

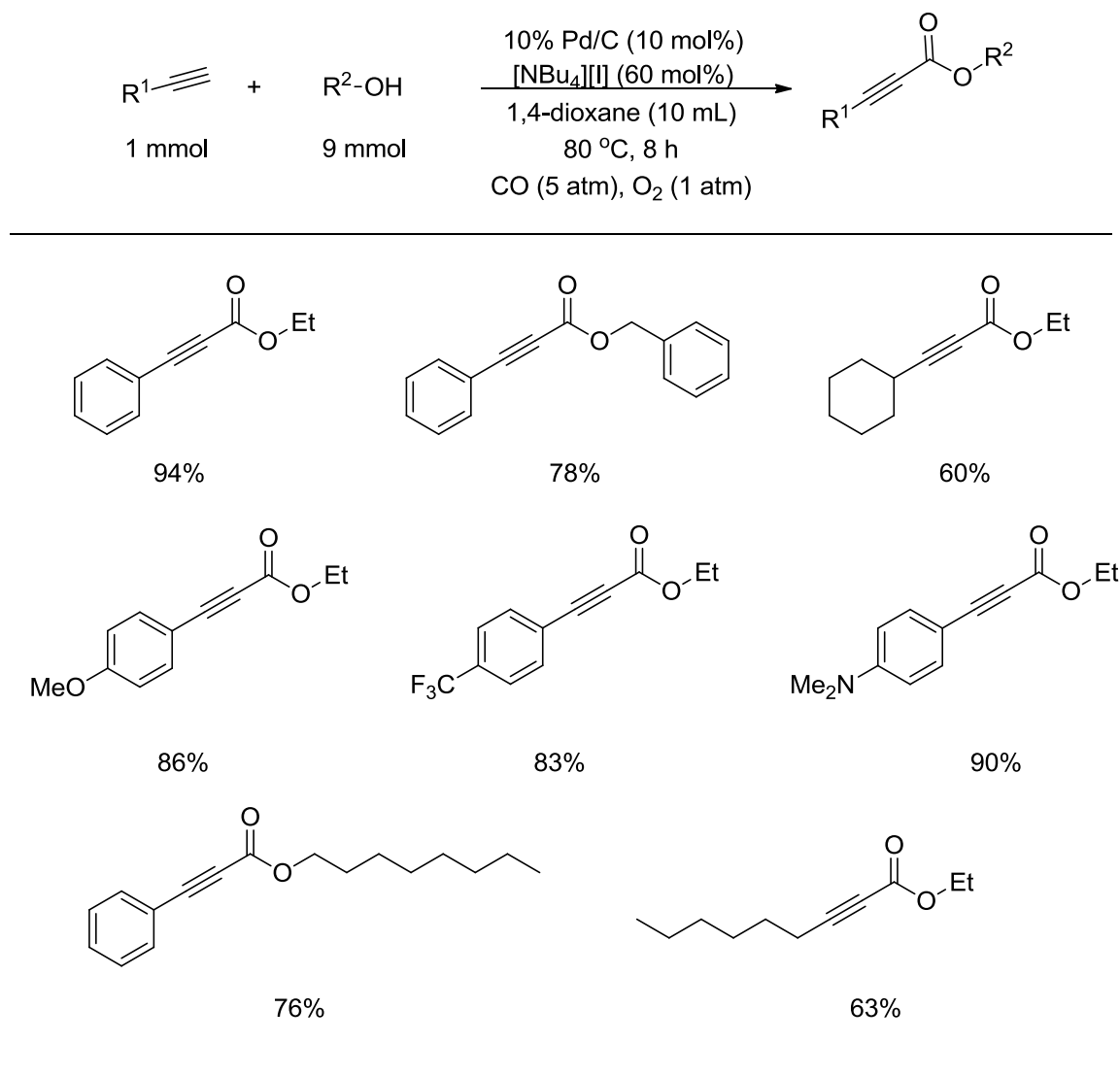


Figure 3.21 Oxidative carbonylation utilising a heterogeneous Pd/C catalyst system.⁴⁰

The authors also demonstrated that when carrying out the reaction using only alcohol as the solvent, the maleate ester was formed. The catalyst could be recycled up to six times with only a 5% loss in activity. This system is a good demonstration of the ability to use a heterogeneous catalyst to facilitate

catalyst recycling, however it still has significant drawbacks, such as the use of 1,4-dioxane as a solvent, and a substantial excess of alcohol is required.

The examples discussed illustrate the potential for the use of oxidative carbonylation in the synthesis of 2-alkynoates, however the methods to date still have several drawbacks.

3.2 Aims and Objectives

It is evident from the literature discussed that oxidative carbonylations could be an invaluable synthetic method in both an academic and industrial arena, with aspects such as inexpensive starting materials and the use of molecular oxygen or air as the terminal oxidant being considered major advantages. However, despite this the systems reported still have several limitations which would undoubtedly hinder their wider application. The systems discussed require 5-10 mol% palladium, which is too high a loading to consider industrial scale up, not to mention the need to employ the alcohol substrate in large excess, therefore limiting the substrate scope to 'simple' inexpensive alcohols. In addition, should a solvent be used, they tend to be ethereal solvents that are deemed unsuitable under oxidative conditions due to safety concerns. The aims of this chapter are to amend these issues to make a safer, more scalable oxidative carbonylation method for the synthesis of 2-alkynoates. This includes the intention to lower the palladium catalyst loading and employ a safer, greener solvent, which should in turn allow for the use of more complex alcohols, with the aim to expand the substrate scope to secondary substrates. Furthermore, we hope to use oxygen or air as the terminal oxidant in a safer manner than that reported previously.

3.3 Results and Discussion

A previous member of the Muldoon group, Qun Cao, optimised a reaction system for the synthesis of 2-alkynoates. The extensive optimisation included the application of ligands, reaction solvent, use of additives, reaction temperature and gas composition. The optimised conditions can be seen in Figure 3.22. Herein shall be discussed aspects of the optimisation that prompted further investigation, followed by a substrate scope.

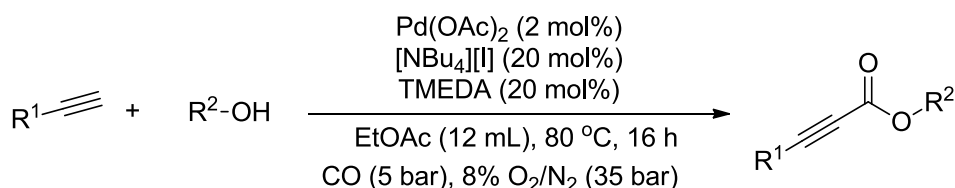
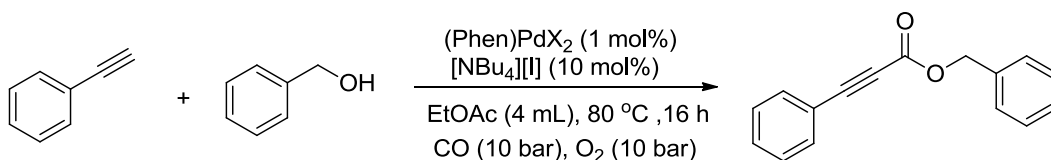


Figure 3.22 Optimised conditions for the synthesis of 2-alkynoates.

During the initial optimisation of the palladium counterion, it was found that acetate was a key reaction component. The results reported by Qun Cao can be seen below.

Table 3.1 Optimisation of palladium salt by Qun Cao.



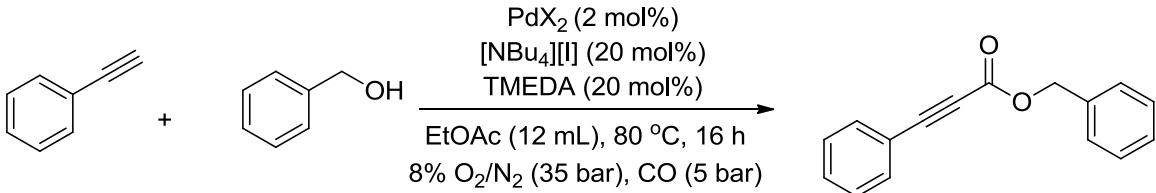
Palladium Catalyst	Conversion of alkyne [%] ^a	Conversion of alcohol [%] ^a	Yield of product [%] ^a
(Phen)Pd(OAc) ₂	32	32	32
(Phen)Pd(MeCN) ₂ (OTf) ₂	0	0	0
(Phen)Pd(CF ₃ COO) ₂	0	0	0
(Phen)PdI ₂	0	0	0

[a] Conversion and yield were determined by GC using biphenyl as internal standard

It was observed that a yield could only be obtained by employing acetate as the counterion, with all others showing no activity. For this reason, Pd(OAc)₂ was chosen for the remainder of the study, however we wished to investigate

it further. During the initial optimisation a phenanthroline palladium complex was used, however it was later found that *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was a preferred ligand, and so we wanted to confirm the palladium salt results under the final optimised reaction conditions. These results are shown in Table 3.2 below.

Table 3.2 Palladium salts under final optimised reaction conditions.

			
Catalyst	Conv. alkyne [%] ^a	Conv. alcohol [%] ^a	Yield of product [%] ^a
PdI ₂	6	0	0
PdCl ₂	12	0	0
Pd(CF ₃ COO) ₂	27	5	0
Pd(OAc) ₂ ^[b]	92	89	82
Pd(OAc) ₂ ^[c]	75	80	73
Pd[(CH ₃) ₃ COO] ₂	90	87	84
Pd(C ₂ H ₅ COO) ₂	80	89	74

[a] Conversion and yield were determined by GC using biphenyl as internal standard.

[b] Pd(OAc)₂ with purity ≥ 99.9%, trace metal basis, purchased from Sigma Aldrich.

[c] Pd(OAc)₂ with purity 99%, purchased from Fluorochem.

As can be seen above, yields were only achieved with acetate and similar carboxylate anions, such as propionate and pivalate. Initially we postulated that the acetate may be necessary to activate the terminal alkyne at the start of the reaction. Acetate has been shown previously to act as an internal base under similar reaction conditions for the hydration⁴¹ and dimerisation⁴² reactions of terminal alkynes. However, we later discovered that when utilising an amine as the nucleophile, acetate was no longer a necessary component which would suggest that its role is intrinsically linked to the alcohol. It may be the case that the acetate is required to deprotonate the alcohol, as is commonly observed in palladium catalysed alcohol oxidation.⁴³

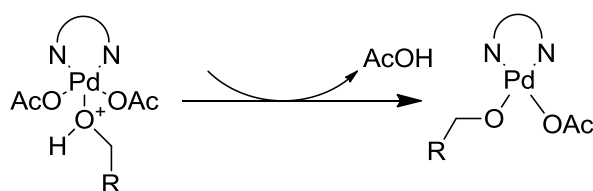
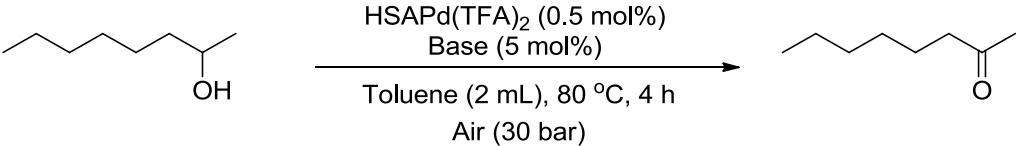


Figure 3.23 Deprotonation of alcohol by acetate.⁴³

In order to confirm this theory, we tried a control reaction with PdCl_2 , whereby 30 mol% sodium acetate was added, to give a 26% yield. This supports the idea that acetate is required for alcohol deprotonation, as the exogenous acetate still produces the desired product, however its exogenous nature means that it cannot be as efficient. We were also interested in testing other exogenous bases to see if the same result was achieved. We tested a nucleophilic base, triethylamine, and a non-nucleophilic base, diisopropylethylamine (DIEA). It was considered that a nucleophilic amine may co-ordinate too strongly to the palladium and result in the deactivation of the catalyst system. In both cases, a negligible yield of 2-3 mol% 2-alkynoate was produced. This result suggests that the acetate is only successful for deprotonation due to its ability to co-ordinate to the palladium centre, however is still labile enough to be lost as acetic acid.

We hoped to demonstrate this by using a palladium(II) alcohol oxidation system, previously reported by the Muldoon group, whereby tetrabutylammonium acetate $[\text{NBu}_4][\text{OAc}]$ is employed as a base.⁴⁴ Usually $\text{Pd}(\text{OAc})_2$ is used as the palladium salt in this reaction, however to test the effectiveness of the base additive for alcohol deprotonation, we used $\text{Pd}(\text{TFA})_2$ (palladium(II) trifluoroacetate) as the fluorine groups cause the acetate to act as a poor base. The results can be seen in Table 3.3.

Table 3.3 Testing bases for Pd(II) alcohol oxidation.

<div><div></div></div>		
Base	Conversion of Alcohol [%] ^a	Yield of Ketone [%] ^a
None	8	2
[NBu ₄][OAc]	99	95
DIEA	22	17

[a] Conversion and yield were determined by GC using biphenyl as an internal standard.

As can be seen above, the reaction does not work in the absence of a suitable base. In the case of [NBu₄][OAc] the reaction achieves a high yield. It is assumed that in this case, the acetate anion can co-ordinate to the palladium centre and facilitate inner sphere deprotonation.⁴³ In the case of the bulky, non-nucleophilic base, DIEA, co-ordination is much less likely, due to the sterically hindering isopropyl groups. It seems that the base can therefore not perform the deprotonation, resulting in a dramatically lower yield. This is further evidence to support our belief that acetate is required for the synthesis of 2-alkynoates to facilitate alcohol deprotonation. It has been shown here that DIEA cannot achieve the same results as [NBu₄][OAc] in alcohol oxidation, suggesting that it cannot carry out deprotonation in our reaction system, explaining why such a low yield is achieved when employing the aforementioned base with palladium(II) chloride.

In addition, control experiments were carried out with 1-phenylethanol, in the absence of alkyne under the carbonylation conditions. In one case CO was also omitted from the reaction. Under both sets of altered conditions, no alcohol oxidation was observed. This shows that no alcohol side reaction is occurring under the optimised reaction conditions, however this may be due to the absence of other steps such as β -hydride elimination.

During the testing of palladium salts, we also observed the importance of palladium salt purity. For example, when comparing $\text{Pd}(\text{OAc})_2$ 99.9% purity with $\text{Pd}(\text{OAc})_2$ >99% purity, a 10% increase in yield could be achieved with the higher purity salt. We wanted to further understand the reason for this. There have been many reports within the literature recently which discuss the inconsistency in the purity of $\text{Pd}(\text{OAc})_2$.⁴⁵ A recent review on palladium acetate examined it from a user's perspective and highlighted ways in which $\text{Pd}(\text{OAc})_2$ purity could be further understood.⁴⁶ They highlighted that the three most common forms of $\text{Pd}(\text{OAc})_2$ are $\text{Pd}_3(\text{OAc})_6$, and the two highest observed impurities, $\text{Pd}_3(\text{OAc})_5(\text{NO}_2)$ and $[\text{Pd}(\text{OAc})_2]_n$. The nitrite impurity arises from the way in which $\text{Pd}(\text{OAc})_2$ is synthesised, whereby glacial acetic acid and palladium powder are refluxed in the presence of nitric acid.⁴⁷ Within this review it was shown how $\text{Pd}(\text{OAc})_2$ purity could be assessed by using NMR,⁴⁸ IR and a solubility test. These methods were then applied with our two samples of commercially available $\text{Pd}(\text{OAc})_2$ to understand the reasoning behind the observed decreased yield. We started by performing IR on both samples, as it had previously been reported which peaks would correspond to the relative impurities in $\text{Pd}_3(\text{OAc})_5(\text{NO}_2)$ ⁴⁹ and $[\text{Pd}(\text{OAc})_2]_n$.⁴⁶ The IR spectra obtained can be seen in Figure 3.24.

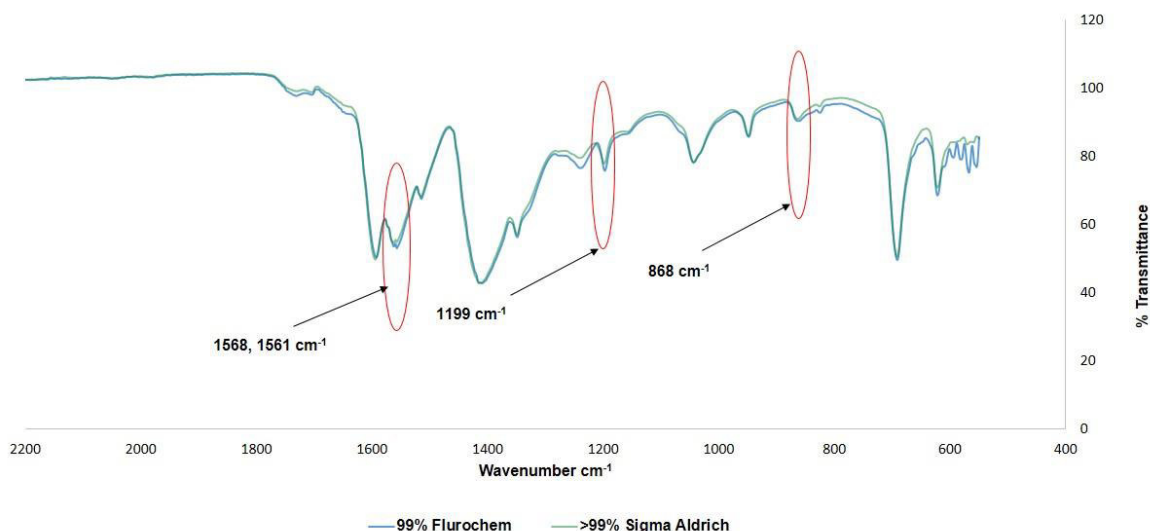


Figure 3.24 IR spectra of commercially available samples of Pd(OAc)₂. Pd(OAc)₂ >99.9% purity purchased from Sigma Aldrich, and Pd(OAc)₂ 99% purity purchased from Fluorochem.

As can be seen from the spectra in Figure 3.24, both samples indicate the presence of Pd₃(OAc)₅(NO₂). These peaks are circled in red for clarity. Neither of the IR samples indicated the presence of [Pd(OAc)₂]_n. However, as IR can only detect above 1% impurity, the samples were then tested for the presence of the polymeric impurity by a solubility test. In this case, 0.1 g of each sample was dissolved in HPLC grade acetone, and then filtered. If the polymeric impurity was present, it should remain as an insoluble filtrate, however in the case of both samples, no polymeric impurity was observed. Both samples were analysed by NMR in anhydrous CDCl₃. It had previously been shown that if the deuterated NMR solvent contained water, this could further complicate the observed spectra due to the facile hydrolysis of Pd(OAc)₂, resulting in the formation of five additional peaks.⁴⁶ In an attempt to overcome this, the freshly purchased deuterated solvent was treated with activated molecular sieves for 24 hours prior to use. The observed NMR spectra can be seen below in Figure 3.25.

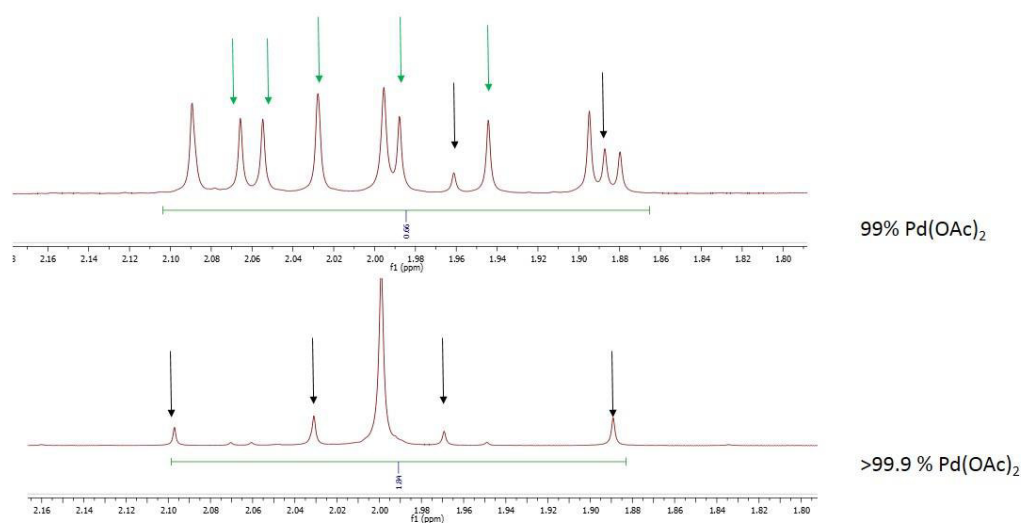
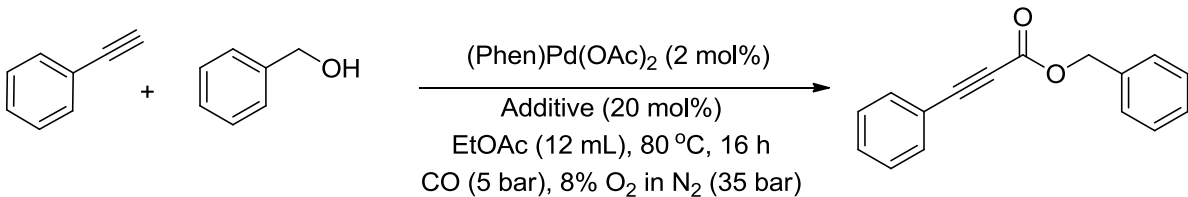


Figure 3.25 ^1H -NMR spectra in CDCl_3 of commercially available samples of $\text{Pd}(\text{OAc})_2$. $\text{Pd}(\text{OAc})_2$ >99.9% purity purchased from Sigma Aldrich, and $\text{Pd}(\text{OAc})_2$ 99% purity purchased from Fluorochem.

The black arrows present in both spectra are representative of acetate hydrolysis. The green arrows highlight five new peaks in the $\text{Pd}(\text{OAc})_2$ sample of 99% purity indicating the presence of $\text{Pd}_3(\text{OAc})_5(\text{NO}_2)$. When integrated against methyl benzoate as an internal standard, it was possible to calculate that the 99% pure $\text{Pd}(\text{OAc})_2$, was in fact only 77% pure $\text{Pd}(\text{OAc})_2$. In contrast, the >99% pure $\text{Pd}(\text{OAc})_2$ was calculated to be 100% $\text{Pd}(\text{OAc})_2$. In conclusion, it is evident that the impurity present in the $\text{Pd}(\text{OAc})_2$ 99% purity is attributed to the replacement of an acetate by nitrite, and as a result, this causes a decrease in yield of the desired 2-alkynoate when employed under our reaction conditions. It is not clear why this may be the case, in some palladium chemistry, the presence of NO_x is known to improve the efficacy of the system⁴⁵ in a similar manner to impurities in $[\text{Pd}_2(\text{dba})_3]$.⁵⁰ However, under our reaction conditions, the presence of NO_x appears to have a negative effect, this may be that the equilibria observed with NO_x chemistry complicates the already complex oxidative equilibria present here.

During the reaction optimisation, it was also observed that iodide was a key additive. Iodide has been shown previously to be a vital component in oxidative carbonylations. For example, tetrabutylammonium iodide [NBu₄][I] was added as an additive in the heterogeneous Pd/C system proposed by Gadge and Bhanage.⁴⁰ The results of various iodide additives employed in our system, observed by Qun Cao can be seen in Table 3.4.

Table 3.4 Effect of halide additives on reaction system. Results shown are from experiments performed by Qun Cao.



Additive	Alkyne Conversion [%] ^a	Alcohol Conversion [%] ^a	Yield [%] ^a
N/A	40	6	5
[NBu ₄][I]	32	32	32
[NBu ₄][Br]	52	16	12
[NBu ₄][OAc]	15	5	2
KI	35	2	2

[a] Conversion and yield were calculated by GC using biphenyl as an internal standard.

As can be seen, the reaction with [NBu₄][Br] displays a higher alkyne conversion than [NBu₄][I], however the iodide analogue demonstrates 100% selectivity, therefore causing it to be preferable. Once it was found that iodide was the best halide, we wished to test KI, as it was tested in previous studies. However, as shown in Table 3.4, the yield obtained was virtually zero. It is likely that this is due to the enhanced solubility of [NBu₄][I] in the chosen reaction solvent, ethyl acetate. Despite iodide having been shown to be a key additive in oxidative carbonylations, its role in the reaction is not yet understood. It is postulated that it may be present to aid the oxidation of Pd(0),

as is shown in Figure 3.26.⁵¹ If this is the case then the reaction should proceed with stoichiometric amounts of iodine, in the absence of oxygen.

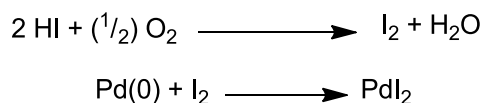


Figure 3.26 Suggested role of iodide within the reaction system.⁵¹

However, when tested under the conditions shown below, only a 25% yield of product was observed. This is further investigated in Chapter 4.

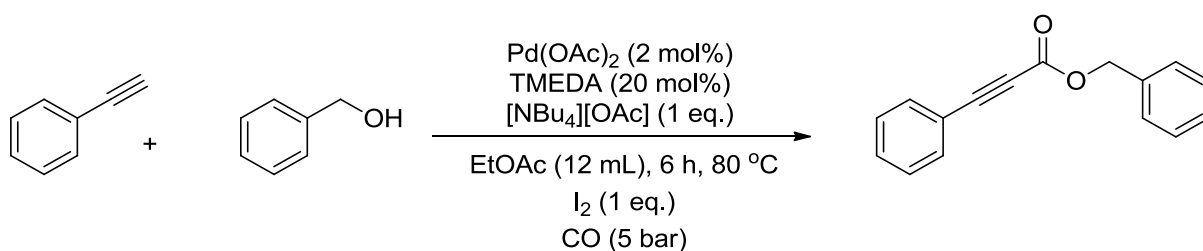


Figure 3.27 Synthesis of 2-alkynoates with stoichiometric iodine.

As mentioned previously, 2-alkynoates can be synthesised *via* carboxylative coupling from terminal alkynes and alkyl halides in combination with CO_2 .²¹⁻³⁰ It could be suggested that under the reaction conditions optimised here, the CO becomes oxidised to CO_2 , and the alcohol undergoes a substitution reaction with the iodide salt to form an alkyl halide. As a result, the 2-alkynoate product would be observed. (Figure 3.28)

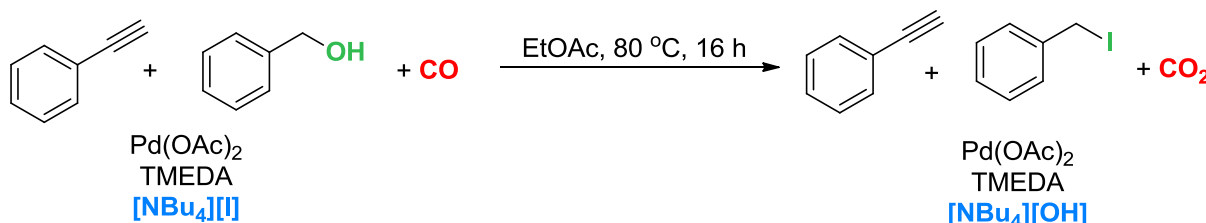


Figure 3.28 Possible synthesis of 2-alkynoates *via* carboxylative coupling.

In order to disprove this theory, two control experiments were performed. The first was in the absence of a palladium salt, as carboxylative coupling does not require palladium, however a second reaction was run in the presence of a pre-isolated palladium-phenanthroline complex, as original optimisation was carried out using the aforementioned complex. Both reactions were run using a dilute oxygen mixture of (8:92) O₂:CO₂. The results can be seen in Figure 3.29 below.

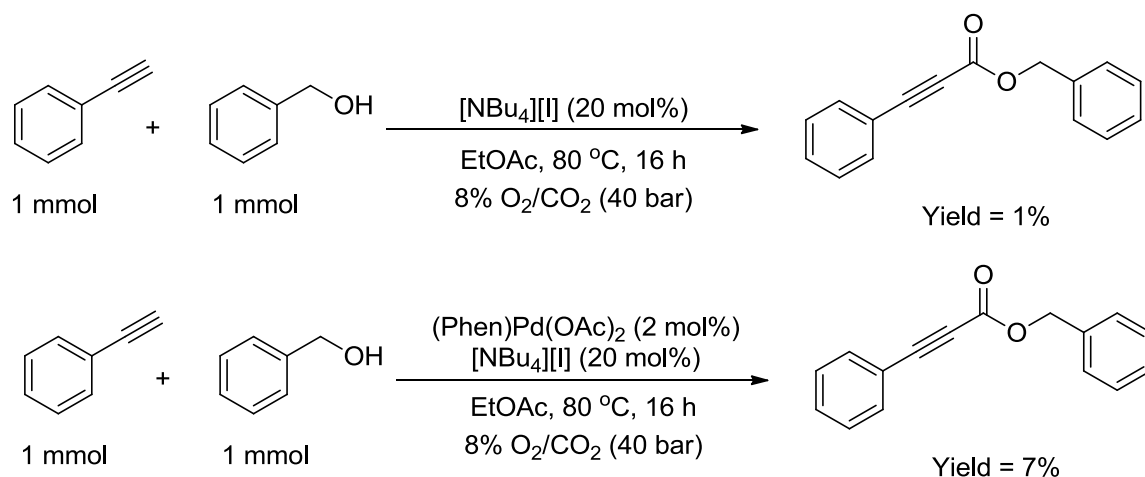


Figure 3.29 Controls experiments to test for carboxylative coupling.

In the case of the reaction without any palladium, virtually no desired product was formed. When palladium was present in the reaction system, only a small amount of product was observed. The conversion of phenylacetylene was higher (20%), however this can be attributed to a side reaction of alkyne dimerisation. These reactions confirmed that the reaction is not proceeding by carboxylative coupling, and that as intended, oxidative carbonylation is occurring.

Once the reaction optimisation was complete, a substrate scope was carried out. As discussed, a major drawback with the previously reported literature was the limitations in substrate scope. This could firstly be attributed to the need to use the alcohol substrate as a solvent, thus limiting the reaction to 'simple', inexpensive alcohols. This is something we can now overcome, as the optimised reaction conditions allow for a 1:1 ratio of alkyne: alcohol, when

employing ethyl acetate as the solvent. A substrate scope with a variety of primary alcohols can be seen in Figure 3.30 below.

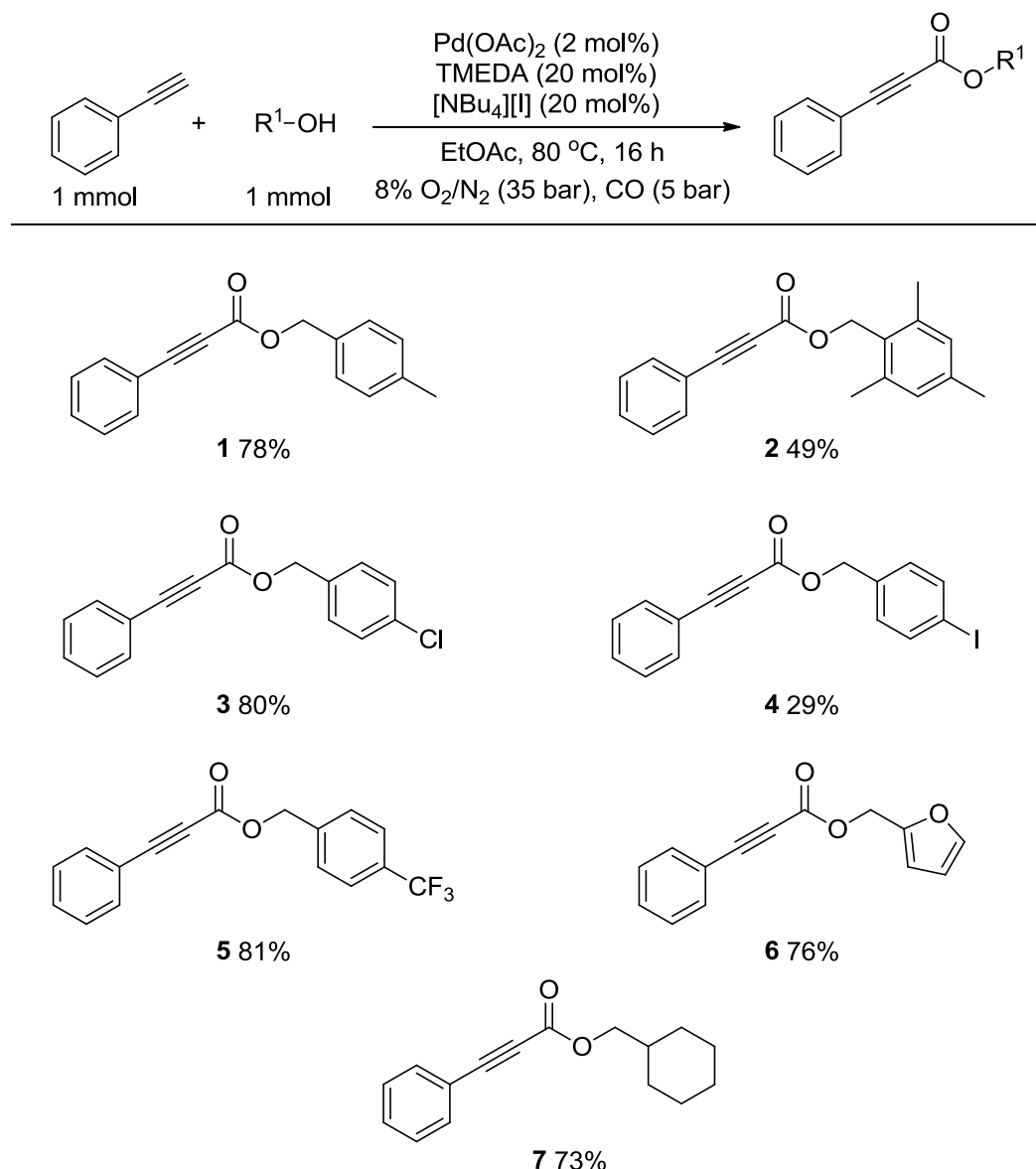
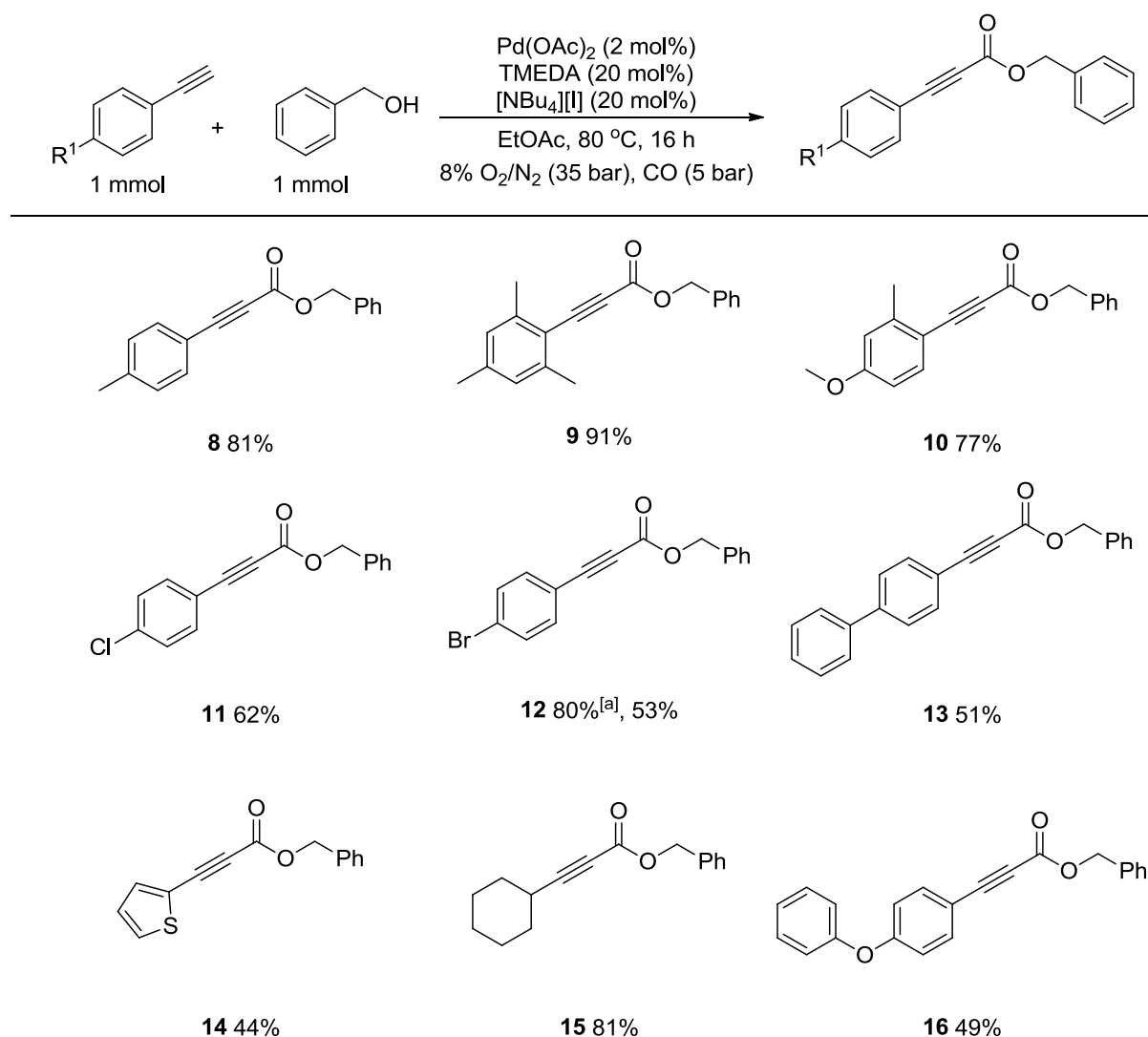


Figure 3.30 Substrate scope of primary alcohols under optimised reaction conditions. All yields shown are isolated yields.

As can be seen from the substrate scope, the optimised conditions work well with both electron donating and electron withdrawing groups, with little preference being observed between substituents. In the case of 2, 4, 6-trimethylbenzyl alcohol, the product (**2**) yield is lower, however this is to be expected with such a sterically hindered alcohol. Aliphatic alcohols such as cyclohexylmethanol could also be employed to achieve high yields (**7**). The

system was also shown to be tolerant of heteroatoms, such as oxygen, as shown in (**6**). We then wished to test various alkynes, as a substrate scope of substituted alkynes had not been shown previously in the literature to the best of our knowledge. The results can be seen in Figure 3.31.



[a] 80% yield when using 1:2 ratio of alkyne to alcohol.

Figure 3.31 Substrate scope of alkynes with benzyl alcohol under optimised reaction conditions. All yields shown are isolated yields.

Similar patterns were observed with the alkyne substrate scope, as those previously seen with the alcohols. A variety of substituted phenylacetylenes containing both electron withdrawing and electron donating groups provided fair to good yields. It was interesting to note that in some cases, such as 4'-bromophenylacetylene (**12**), it was necessary to increase the ratio of alkyne to

alcohol to 1:2 in order to achieve the same yield as that with the 4'-bromobenzyl alcohol. The system was shown to be heteroatom tolerant (**14**), and could be applied to sterically hindered alkynes as in the case of (**9**).

The second major limitation in the substrate scope for the synthesis of 2-alkynoates was the inability to use secondary alcohols. We found this could be overcome by using a ratio of 1:2 alkyne to alcohol and increasing the catalyst loadings to 3 mol% Pd(OAc)₂, 30 mol% TMEDA and 30 mol% [NBu₄][I]. We also showed that it was possible to retain chirality during the reaction, as is shown in Figure 3.32 below.

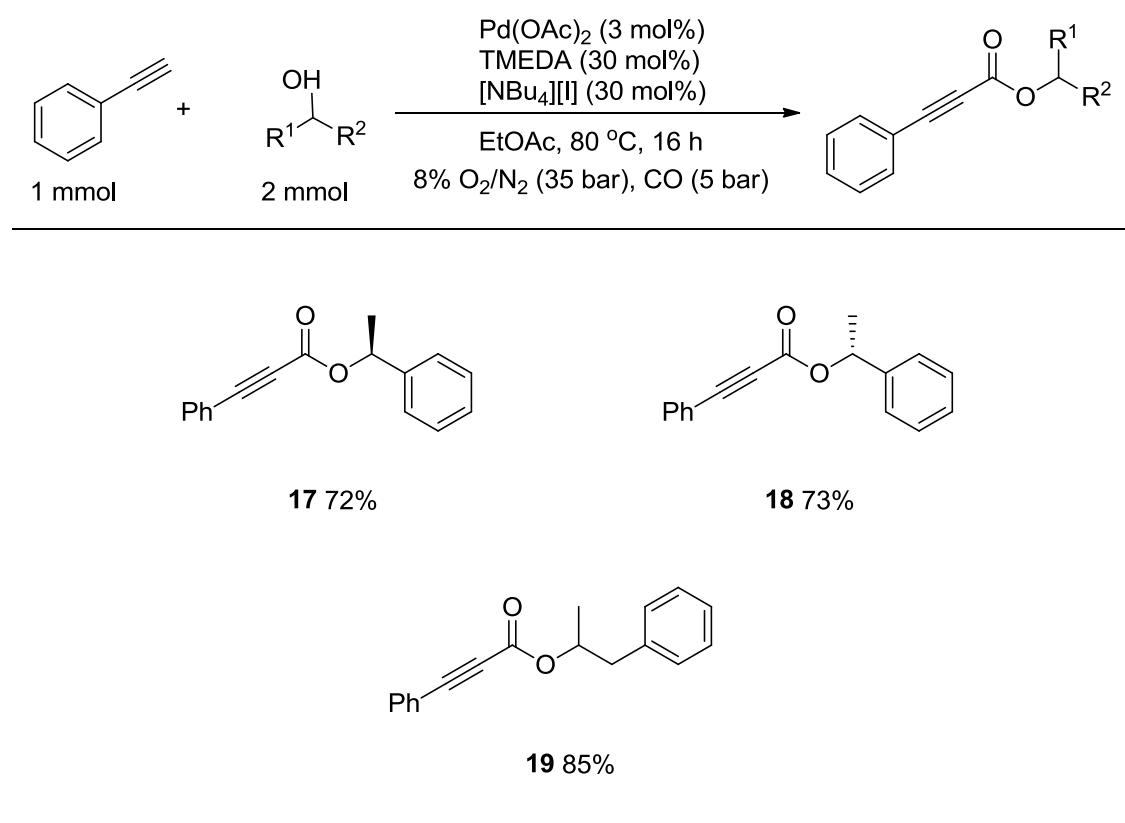


Figure 3.32 Substrate scope of secondary alcohols under optimised reaction conditions. All yields shown are isolated yields.

The ability to employ secondary alcohols under our optimised reaction conditions was particularly pleasing as this had not been possible with previously reported systems.

To date, there has not been any in depth study carried out regarding the mechanism of the reaction. Yamamoto and co-workers postulated the reaction mechanism³⁹ to be as shown in Figure 3.33, however this was not based on kinetic studies and more on the synthesis of potential reaction intermediates.

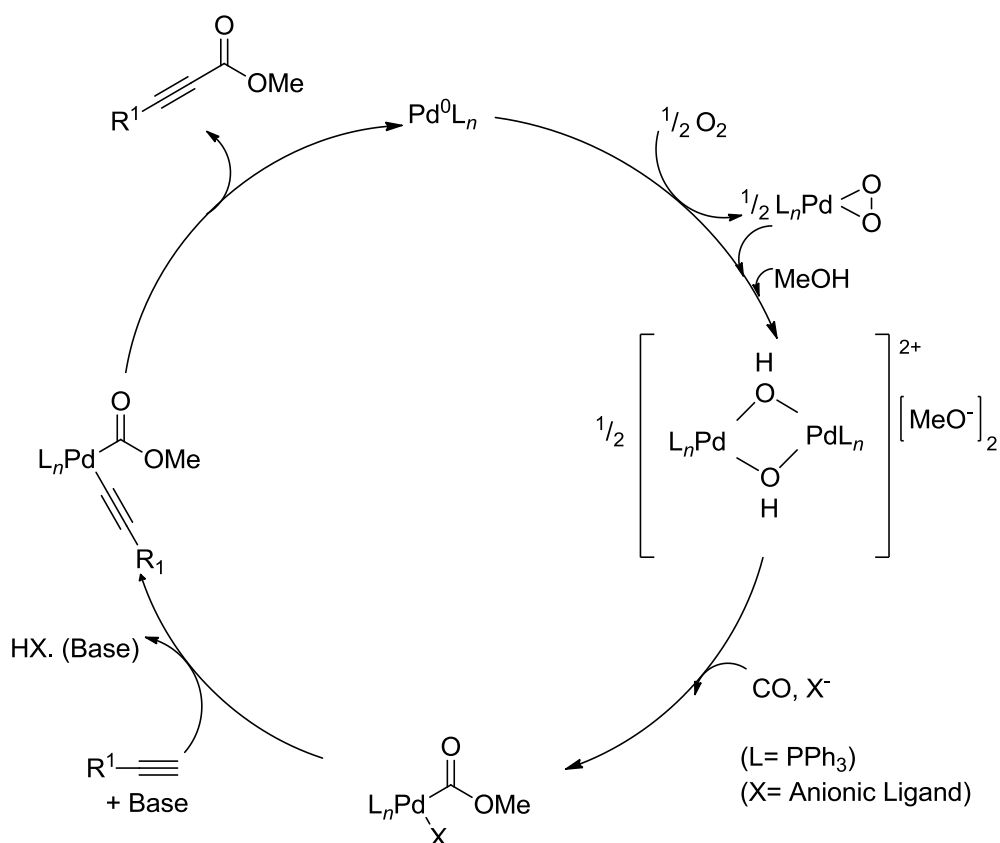


Figure 3.33 Reaction mechanism suggested by Yamamoto and co-workers.³⁹

The work performed here does not contradict this suggested mechanism, however more so highlights the need for kinetic mechanistic investigations to aid further understanding of this complex reaction system, if more effective second generation catalysts are to be designed.

One of the pre-existing problems with regards to oxidative carbonylation is the need for high palladium catalyst loadings. This problem has been addressed within this work, with catalyst loadings lowered to 2-3 mol%, however in order to be industrially viable, there is a need for the palladium catalyst to be recycled. Whereas this has not been studied here, it holds importance when

considering the sustainability of the reaction system, and would be imperative regarding future work.

3.4 Conclusion

A new system for the oxidative carbonylation of alcohols and terminal alkynes with CO has been developed which overcomes many of the drawbacks associated with previously reported methods. The system uses a lower palladium catalyst loading and negates the use of phosphine ligands. In addition, the alcohol substrate is no longer required for use as a solvent and can be used in a 1:1 or 1:2 ratio to the alkyne. An industrially recommended, green solvent, ethyl acetate has been employed and the reaction can be operated under dilute oxygen mixtures, resulting in a safer reaction system than the preceding literature. This is a major improvement on previous systems that required the use of ethereal solvents such as 1,4-dioxane, and were run under high pressures of pure oxygen. The substrate scope was also extended to a wide variety of primary alcohols in combination with a range of alkynes and the system can also be utilised with secondary alcohols which had not previously been achieved.

After the publication of this work, Gabriele and co-workers reported a system for the preparation of 2-alkynoates and maleic derivatives from terminal and internal alkynes respectively.⁵² Their catalytic method used bulky bidentate nitrogen donating ligands, in combination with AgOTf and employed benzoquinone as the terminal oxidant.

The optimised system was applied to a variety of terminal aromatic and aliphatic alkynes to produce high yields. With regards to alcohols, bulky alcohols such as *tert*-butanol could be applied, in addition to others such as isopropanol and cyclopentanol. Their optimised reaction conditions and a selection from the substrate scope can be seen in Figure 3.34. When testing internal alkynes under the same conditions, a mixture of products were obtained including the maleic diester and their cyclic isomers, with the ratio of these products being dependent on the nature of the substrates. However, it was also found that the cyclic product could be readily converted to the maleic diester by acid catalysed isomerisation in methanol.⁵²

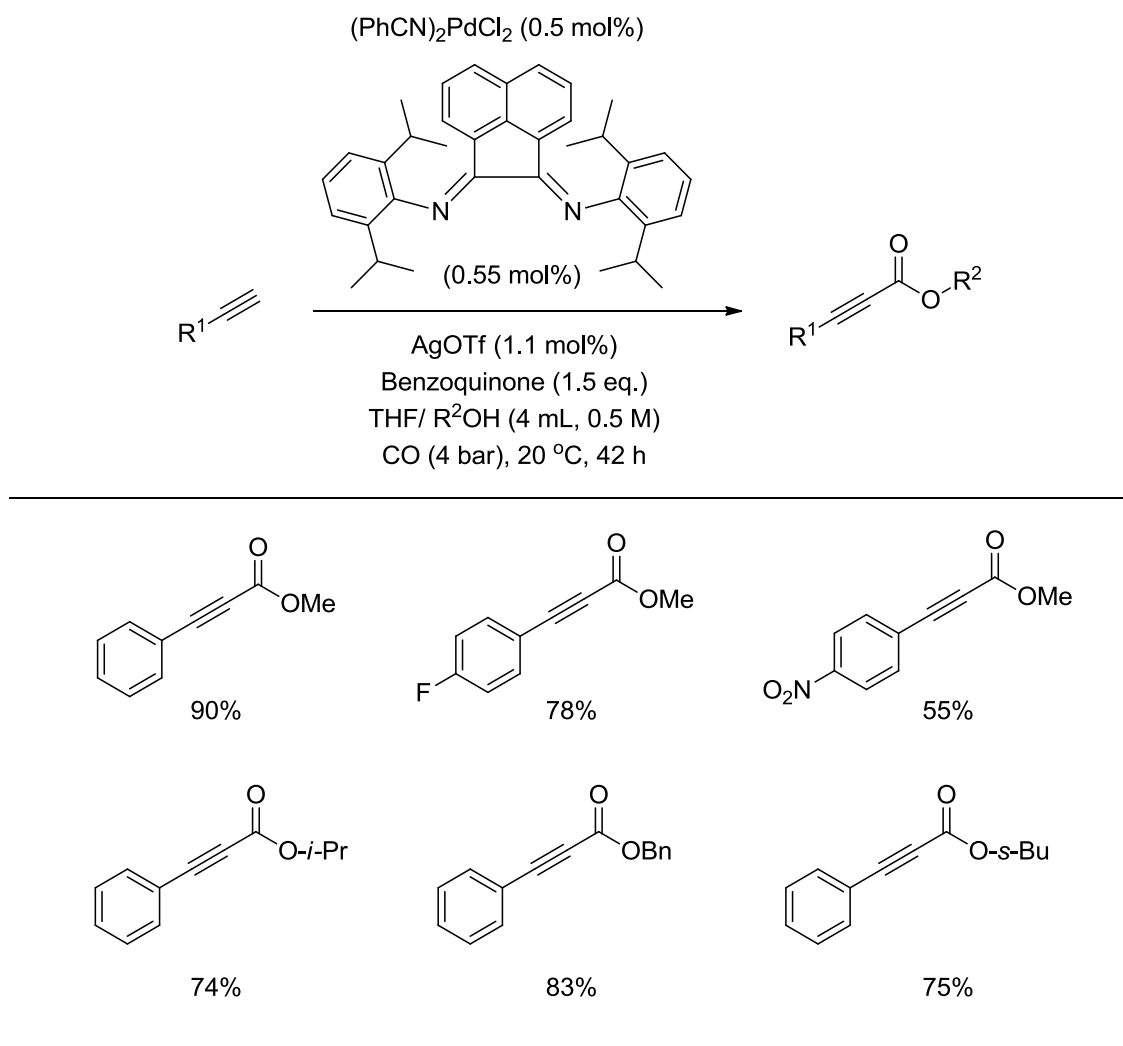


Figure 3.34 Gabriele conditions for mono-alkoxycarbonylation of terminal alkynes.⁵²

This system was applicable to similar substrates as those demonstrated within our work, achieving similar yields but requiring a prolonged reaction time. This method still requires an excess of alcohol, and uses benzoquinone as the terminal oxidant. In addition, THF is employed as the solvent, which although this is not as large a problem here as in other methods as oxygen is not used, remains ill- advised for use industrially due to the necessary precautions required in terms of storage and transport.

3.5 Experimental

3.5.1 General Considerations

Unless otherwise stated, all reagents were purchased from Sigma-Aldrich and used without further purification. The following chemicals were purchased from Fluorochem: 4-chlorophenylacetylene, 4-bromophenylacetylene, ethynylcyclohexane, (4-chlorophenyl)methanol, (4-iodophenyl)methanol, 4-ethynyl-1,1'-biphenyl, and palladium(II) acetate (99%). The following chemicals were purchased from Alfa Aesar: palladium(II) trifluoroacetate (97%), and palladium(II) trimethylacetate (97%). The following palladium salts were purchased from Sigma Aldrich: palladium(II) propionate ($\geq 99.5\%$), palladium(II) acetate (≥ 99.9 trace metal basis), palladium(II) chloride ($\geq 99.9\%$), palladium(II) iodide ($\geq 99.9\%$). Carbon monoxide (CP Grade), air and O₂ cylinders were from BOC and pre-mixed O₂:N₂(8:92) (β standard) and O₂:CO₂(8:92) (β standard) cylinders were from BOC Special Gases.

All synthesis and reactions were carried out in oven-dried glassware. Any reactions that were monitored by thin layer chromatography were carried out using Merck silica gel 60 sheets and visualised with UV light. Flash column chromatography was performed with 60 Å silica gel as the stationary phase, and all solvents used were of analytical grade.

¹H-NMR spectra were recorded on a Bruker AVX400 (400 MHz) spectrometer at room temperature. ¹³C NMR spectra were recorded on a Bruker AVX400 (101 MHz) spectrometer at room temperature. NMR data is reported as follows; chemical shift is recorded in parts per million (δ , ppm) in deuterated chloroform (CDCl₃) taken as 7.26 ppm. Multiplicity; s= singlet, d=doublet, dd= doublet of doublets, td= triplet of doublets, dt = doublet of triplets, m= multiplet.

Melting points were measured on Stuart melting point apparatus (Digital, SMP10). IR spectra were measured on PerkinElmer Spectrum 100 FT-IR Spectrometers. Mass spectra were recorded on a Waters Micromass LCT Premier spectrometer.

Analysis by Gas Chromatography was performed using an Agilent 6890N series gas chromatograph. An Agilent 19091J-433 HP-5 5% Phenyl Methyl Siloxane capillary (column) (30.0 m x 250 µm x 0.25 µm nominal) was employed for all the separations using the following conditions. Column head pressure, 30 kPa (4.49 psi) helium; initial column temperature, 40 °C; initial hold time, 0 min; rate of temperature ramp 1, 4 °C/min; next temperature, 100 °C; hold time, 0 min; rate of temperature ramp 2, 30 °C/min, final temperature 320 °C; hold time, 15 min; injection temperature, 250 °C; detection temperature, 250 °C. The effluent was combusted in a H₂/Air flame and detected using an FID (flame ionisation detector). Ion count data were sent to a plotter, which integrated the area under the peaks.

Retention of chirality was confirmed by Chiral HPLC. This was carried out on an Agilent 1100 series HPLC, with a Chiralcel® OJ-H column. HPLC conditions: 1 ml/min 95% hexane / 5% isopropanol with a diode array detector measuring at 220 nm.

The conversions and yields reported were calculated by GC using biphenyl as an internal standard. An initial response factor (R_f) was calculated for the particular product or starting material, by dissolving a known amount of analyte and standard (biphenyl) in ether. Then the following equation was used to calculate the R_f value:

$$R_f = \frac{\text{Moles}_{\text{analyte}} \times \text{Area}_{\text{internal standard}}}{\text{Moles}_{\text{internal standard}} \times \text{Area}_{\text{analyte}}}$$

The amount of product or starting material present was then calculated using the following equation:

$$\text{Moles}_{\text{analyte}} = \frac{\text{Moles}_{\text{internal standard}} \times R_f \times \text{Area}_{\text{analyte}}}{\text{Area}_{\text{internal standard}}}$$

3.5.2 Safety Considerations

This work requires the use of carbon monoxide. Only trained personnel should be allowed to work with carbon monoxide cylinders. Carbon monoxide is a toxic, flammable gas. The cylinder was kept in a ventilated cylinder cupboard, fitted with a CO alarm. All tubing and reaction vessels were vented in the fume cupboard. These reactions also use high pressures of air, O₂:N₂ (8:92) or O₂:CO₂(8:92). All reactions were carried out at pressures significantly under the pressure ratings of the reactor vessels. The reactor vessels were also fitted with safety relief valves in case of unprecedented pressure build up.

3.5.3 General Methods

General Considerations

Pd(OAc)₂ which was ≥99.9% trace metal basis purity (from Sigma Aldrich) was used and it was found that lower grades of Pd(OAc)₂ led to reduced yields. TMEDA was added using a stock solution, whereby a fresh stock solution was prepared daily, as reused stock solutions were found to give a reduced yield.

All reactions were carried out in 45 mL pressure vessels which were placed inside a pre-heated aluminium block, on a stirring hotplate. The heating block was thermostatically controlled during the reaction. Unless otherwise stated, all reactions were carried out in a glass liner, with a Teflon coated triangular stir bar.

Optimisation of Catalytic System

Reactions were performed in 45 mL high-pressure reactors made of hastelloy and the reaction mixture was placed in a glass liner, equipped with a magnetic stirrer. To the glass liner, tetrabutylammonium iodide (20 mol%, 0.20 mmol, 0.0739 g) and Pd(OAc)₂ (2 mol%, 0.02 mmol, 0.0045 g) and TMEDA (20 mol%, 0.20 mmol, 0.0232 g) from a stock solution in ethyl acetate (2 mL) were added. The solution was made up to 12 mL with ethyl acetate. This was followed by the addition of alkyne (1 mmol) and alcohol (1 mmol). The glass liner was placed in a reactor and then pressurized with 5 bar of carbon monoxide gas,

followed by O₂:N₂ (8:92) to give a total reaction pressure of 40 bar. The reactor was then stirred on a pre-heated heating block at 80 °C for sixteen hours. Once the reaction was complete, the reactor was cooled in an ice bath and slowly depressurised in a fume hood. Internal standard (biphenyl) (~0.2 g) was added, and the glass liner magnetically stirred for 1 minute to ensure all standard was fully dissolved. A sample was then prepared for GC analysis by filtration through a silica plug with diethyl ether to remove any catalyst components. The sample was then submitted for GC analysis.

Preparation of Isolated Substrates

Primary Alcohols

Procedure was the same as described above, however at the end of the reaction the reactor was cooled and depressurized, then poured into a separating funnel and brine added. The aqueous layer was then separated and back extracted with ethyl acetate twice. The combined organic layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography, and the appropriate fractions combined and concentrated under reduced pressure. The product was then dried under high vacuum.

Secondary Alcohols

Procedure was the same as described above using higher catalyst loadings; tetrabutylammonium iodide (30 mol%, 0.30 mmol, 0.111 g) and Pd(OAc)₂ (3 mol%, 0.03 mmol, 0.0067 g) and TMEDA (30 mol%, 0.30 mmol, 0.0349 g) from a stock solution in ethyl acetate (2 mL) were added. The solution was made up to 12 mL with ethyl acetate. This was followed by the addition of alkyne (1 mmol) and alcohol (2 mmol). At the end of the reaction the reactor was cooled and depressurized, then poured into a separating funnel and brine added. The aqueous layer was then separated and back extracted with ethyl acetate twice. The combined organic layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography, and the appropriate fractions combined and

concentrated under reduced pressure. The product was then dried under high vacuum.

Method for Pd(TFA)₂ Alcohol Oxidation

A stock solution was prepared of Pd(II) trifluoroacetate (0.065 g) and 8-hydroxyquinolinesulfonic acid (0.0474 g) in 20 mL toluene was sonicated until homogenous. To a 16 mL glass liner, was added, 2 mL stock solution, base (5 mol%, 0.195 mmol) and 2-octanol (3.9 mmol, 0.508 g). The glass liner was placed in a 20 mL hastellhoy reactor body, sealed and pressurised with 30 bar Air. The reactor body was then placed in a preheated aluminium heating block at 80 °C for 4 hours. After this time, the reactor was cooled in an ice water bath, and slowly depressurised in a fumecupboard. Biphenyl was added to the reaction solution (0.1 g), and stirred magnetically for 2 minutes to insure all the biphenyl was dissolved. A sample was then prepared for GC analysis by filtration through a short silica plug with diethyl ether.

3.5.4 Analysis of Pd(OAc)₂

IR Analysis

Pd(OAc)₂ 99 % purity IR (neat): 1594, **1562**, 1408, 1349, **1197**, 1052, 950, **869**, 692, 621 cm⁻¹.

Pd(OAc)₂ >99 % purity IR (neat): 1595, **1563**, 1410, 1349, **1199**, 1040, 950, **869**, 692, 621 cm⁻¹.

IR stretches reported in red are indicative of the presence of Pd₃(OAc)₅(NO₂).⁴⁶

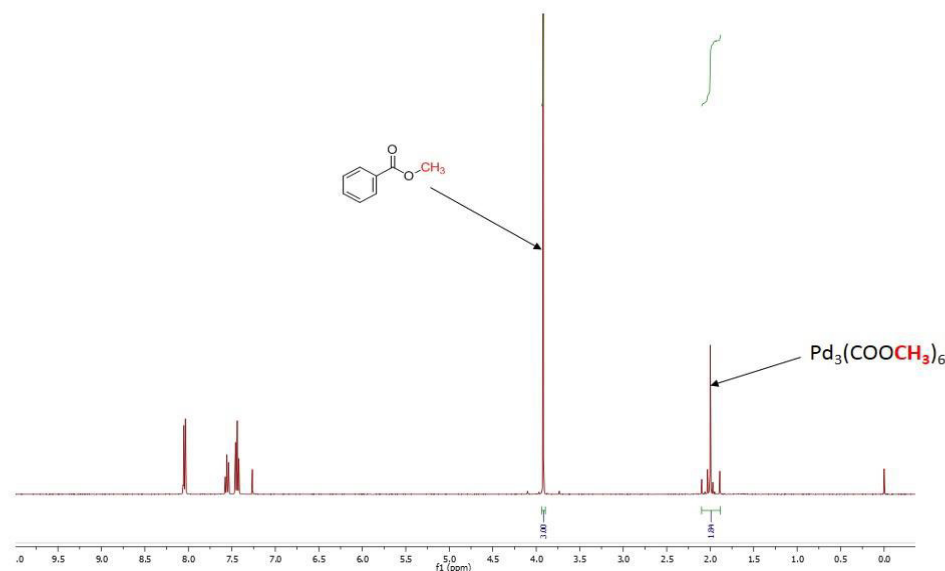
Solubility Test

Each sample (0.1 g) was dissolved in HPLC grade acetone (10 mL). The solution was then filtered by vacuum filtration, and the filter paper weighed before and after filtration. For both samples, no change in mass was observed. This indicated that no polymeric Pd(OAc)₂ was present, as no insoluble residue remained after filtration.

NMR Analysis

Freshly purchased CDCl_3 was dried for 24 hours with activated molecular sieves before use. A known quantity of $\text{Pd}(\text{OAc})_2$ (~ 10 mg) was dissolved in CDCl_3 with a standard (methyl benzoate) of known quantity (~20-30 mg). A sample was taken for ^1H -NMR analysis. Using the integration of the $-\text{CH}_3$ group of the standard, and the (OAc) peak of the $\text{Pd}(\text{OAc})_2$ it was possible to calculate the quantity of pure $\text{Pd}(\text{OAc})_2$ present in the sample.

Example Spectra



Example Calculation

Methyl benzoate = 1 x CH_3

$\text{Pd}_3(\text{OAc})_6$ = 6 x CH_3

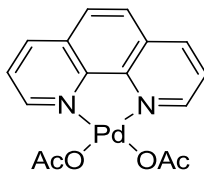
Ratio of CH_3 = 1:6

From integration = 1: 1.84

$1.84 / 6 \times [0.188 \text{ (mmol standard)}] = 0.0576 \text{ mmol Pd}_3(\text{OAc})_6$

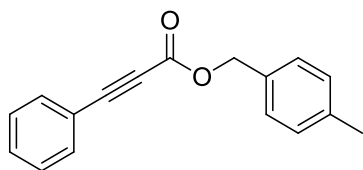
$0.0576 / 0.057 \text{ (mmol Pd in sample)} = 100 \% \text{ Pd}_3(\text{OAc})_6$

3.5.5 Synthesis of Isolated (Phen)Pd(OAc)₂ Complex Applied in CO₂ Testing Reactions



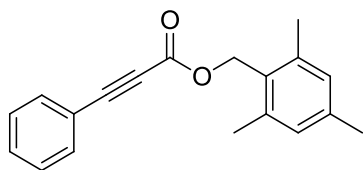
A solution of 1,10-phenanthroline (0.3023 mmol, 0.0545 g) in dichloromethane (2 mL) was added to a solution of palladium(II) acetate (0.2922 mmol, 0.0656 g) in toluene (12 mL) and stirred under a nitrogen atmosphere at room temperature for 3 hours. HPLC grade hexane was then added to precipitate the complex as a bright yellow solid. The solution was then filtered under suction and dried under high vacuum before use. Yield = 0.101 g, 85%. ¹H NMR (400 MHz, CDCl₃): δ 8.61-8.54 (m, 4H), 7.97 (s, 2H), 7.82-7.77 (m, 2H), 2.20 (s, 6H). ¹³C NMR (101 MHz, CDCl₃): δ 178.8, 150.6, 146.7, 138.9, 129.8, 127.3, 125.4, 23.5. Analytical data was in correspondence with the literature.⁵³

3.5.6 Product Characterisation



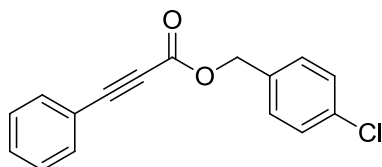
4-Methylbenzyl 3-phenylpropiolate (1)

Purified by flash column chromatography (diethyl ether /petroleum ether = 5: 100) to afford **1** as a golden yellow oil (0.1975 g, 78 %). ¹H NMR (400 MHz, CDCl₃): δ 7.58-7.54 (m, 2H), 7.46-7.40 (m, 1H), 7.39-7.29 (m, 4H), 7.22-7.16 (m, 2H), 5.22 (s, 2H), 2.36 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): 154.1, 138.7, 133.2, 129.5, 129.0, 128.7, 119.8, 86.7, 80.8, 67.9, 21.4. HRMS (ESI⁺) Calc. for C₁₇H₁₄O₂ [M+H⁺] 251.1072, found: 251.1065. IR (neat): 2218, 1704, 1280, 1285, 1164, 756 cm⁻¹.



2,4,6-Trimethylbenzyl 3-phenylpropiolate (2)

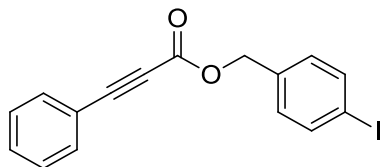
Purified by flash column chromatography (diethyl ether /petroleum ether = 5: 100) to afford **2** as a bright yellow crystalline solid (0.1422 g, 49 %). m.p. 63-65 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.57-7.53 (m, 2H), 7.45-7.40 (m, 1H), 7.38-7.32 (m, 2H), 6.91-6.88 (m, 2H), 5.32 (s, 2H), 2.39 (s, 6H), 2.28 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 154.5, 139.1, 138.6, 133.2, 129.4, 128.7, 128.3, 119.8, 86.6, 80.7, 62.7, 21.2, 19.7. HRMS (ESI⁺) Calc. for C₁₉H₁₉O₂ [M+H⁺] 279.1385, found: 279.1375. IR (neat): 2221, 1703, 1277, 1167, 748, 686 cm⁻¹.



4-Chlorobenzyl 3-phenylpropiolate (3)

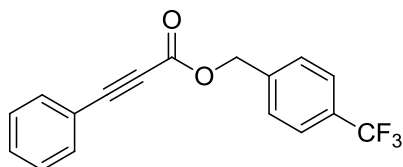
Purified by flash column chromatography (ethyl acetate /petroleum ether = 5: 100) to afford **3** as a white crystalline solid (0.2168 g, 80%). m.p. 59-61 °C. ¹H

NMR (400 MHz, CDCl_3): δ 7.61-7.55 (m, 2H), 7.48-7.42 (m, 1H), 7.40-7.32 (m, 6H), 5.22 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ 153.9, 134.7, 133.6, 133.2, 130.9, 130.1, 129.0, 128.7, 119.6, 87.2, 80.5, 67.0. HRMS (ESI^+) Calc. for $\text{C}_{16}\text{H}_{12}\text{ClO}_2$ $[\text{M}+\text{H}^+]$ 271.0526, found: 271.0494. IR (neat): 2215, 1700, 1489, 1285, 1166, 757 cm^{-1} .



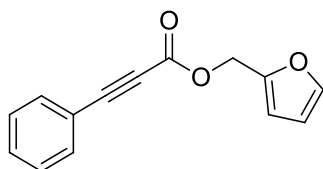
4-Iodobenzyl 3-phenylpropiolate (4)

Purified by flash column chromatography (ethyl acetate /petroleum ether = 5: 100) to afford **4** as a pale yellow oil (0.1068 g, 29 %). ^1H NMR (400 MHz, CDCl_3): δ 7.77-7.71 (m, 2H), 7.62-7.58 (m, 2H), 7.49-7.44 (m, 1H), 7.42-7.36 (t, J = 7.5 Hz, 2H), 7.21-7.16 (d, J = 8.3 Hz, 2H), 5.21 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 153.9, 138.0, 134.8, 133.2, 130.6, 128.8, 119.6, 94.6, 87.3, 80.5, 67.1. HRMS (ESI^+) Calc. for $\text{C}_{16}\text{H}_{15}\text{INO}_2$ $[\text{M}+\text{NH}_4^+]$ 380.0148 found: 380.0163. IR (neat): 2210, 1704, 1283, 1189, 1170, 760 cm^{-1} .



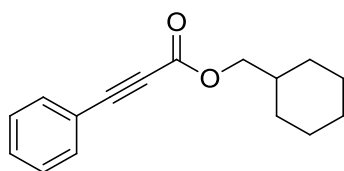
4-(Trifluoromethyl)benzyl 3-phenylpropiolate (5)

Purified by flash column chromatography (diethyl ether/petroleum ether = 5: 100) to afford **5** as a pale yellow crystalline solid (0.2404 g, 81 %). m.p. 50-51 $^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 7.68-7.62 (d, J = 8.1 Hz, 2H), 7.62-7.57 (m, 2H), 7.56-7.52 (d, J = 8.1 Hz, 2H), 7.49-7.43 (m, 1H), 7.41-7.35 (m, 2H), 5.31 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 153.8, 139.1, 133.2, 130.7, 128.6, 125.5, 122.8, 119.5, 87.5, 80.3, 66.7. NMR Data is in correlation with literature.⁵⁴ HRMS (ESI^+) Calc. for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{O}_2$ $[\text{M}+\text{H}^+]$ 305.0789, found: 305.0765. IR (neat): 2218, 1706, 1285, 1191, 1067, 760 cm^{-1} .



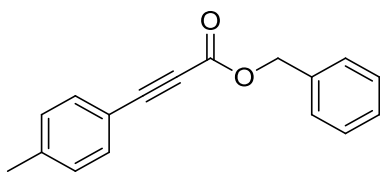
(Tetrahydrofuran-2-yl)methyl 3-phenylpropiolate (**6**)

Purified by flash column chromatography (ethyl acetate /petroleum ether = 5: 100) to afford **6** as a golden yellow oil (0.1692 g, 76 %). ^1H NMR (400 MHz, CDCl_3): δ 7.59-7.53 (m, 2H), 7.47-7.40 (m, 2H), 7.39-7.32 (m, 2H), 6.50-6.47 (d, J = 3.3 Hz, 1H), 6.40-6.36 (dd, J = 1.9, 3.2 Hz, 1H), 5.21 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 153.8, 148.61, 143.7, 133.2, 130.8, 128.7, 119.6, 111.5, 110.9, 87.2, 80.4, 59.4. HRMS (ESI $^+$) Calc. for $\text{C}_{14}\text{H}_{11}\text{O}_3$ $[\text{M}+\text{H}^+]$ 227.0708, found: 227.0705. IR (neat): 2220, 1706, 1280, 1162, 743 cm^{-1} .



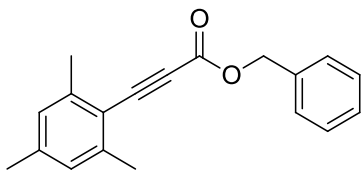
Cyclohexylmethyl 3-phenylpropiolate (**7**)

Purified by flash column chromatography (diethyl ether /petroleum ether = 5: 100) to afford **7** as a pale yellow oil (0.1845 g, 73 %). ^1H NMR (400 MHz, CDCl_3): δ 7.52-7.48 (m, 2H), 7.38-7.33 (m, 1H), 7.31-7.25 (m, 2H), 3.99-3.93 (d, J = 6.6 Hz, 2H), 1.75-1.55 (m, 6H), 1.22-1.07 (m, 3H), 0.98-0.86 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 154.4, 133.1, 130.7, 128.7, 119.8, 86.2, 80.9, 71.2, 37.1, 29.6, 26.3, 25.7. HRMS (ESI $^+$) Calc. for $\text{C}_{16}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}^+]$ 243.1385, found: 243.1388. IR (neat): 2927, 2226, 1705, 1280, 1170, 756 cm^{-1} .



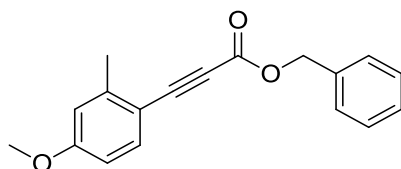
Benzyl 3-(*p*-tolyl)propiolate (**8**)

Purified by flash column chromatography (diethyl ether /petroleum ether = 5: 100) to afford **8** as a dark yellow solid (0.1951 g, 81 %). m.p. 72-75 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.49-7.45 (d, J = 8.0 Hz, 2H), 7.44-7.33 (m, 5H), 7.20-7.14 (d, J = 7.9 Hz, 2H), 5.26 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 154.2, 141.6, 135.2, 133.2, 129.6, 128.8, 116.6, 87.5, 80.4, 68.8, 21.9. NMR data is consistent with literature values.⁵⁴ HRMS (ESI⁺) Calc. for $\text{C}_{17}\text{H}_{15}\text{O}_2$ [$\text{M}+\text{H}^+$] 251.1072, found: 251.1082. IR (neat): 2215, 1695, 1288, 1166, 756 cm^{-1} .



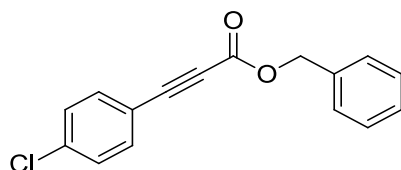
Benzyl 3-mesitylpropiolate (**9**)

Purified by flash column chromatography (diethyl ether /petroleum ether = 5: 100) to afford **9** as a golden orange oil (0.2552 g, 91 %). ^1H NMR (400 MHz, CDCl_3): δ 7.44-7.32 (m, 5H), 6.90-6.84 (s, 2H), 5.27 (s, 2H), 2.45-2.41 (d, J = 4.5 Hz, 6H), 2.30-2.26 (d, J = 9.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 154.5, 142.7, 140.8, 135.4, 128.8, 128.6, 128.1, 116.6, 88.1, 85.5, 67.6, 21.6, 20.9. HRMS (ESI⁺) Calc. for $\text{C}_{19}\text{H}_{19}\text{O}_2$ [$\text{M}+\text{H}^+$] 279.1385, found: 279.1387. IR (neat): 2212, 1701, 1265, 1206, 1147, 752 cm^{-1} .



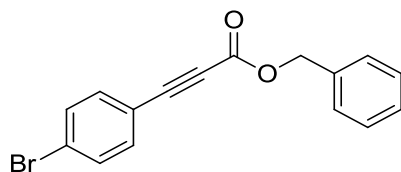
Benzyl 3-(4-methoxy-2-methylphenyl)propiolate (**10**)

Purified by flash column chromatography (ethyl acetate /petroleum ether = 10: 100) to afford **10** as an off white solid (0.2150 g, 77 %). m.p. 38-39 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.50-7.46 (d, J = 8.5 Hz, 1H), 7.44-7.32 (m, 5H), 6.76-6.74 (m, 1H), 6.73-6.68 (m, 1H), 5.26 (s, 2H), 3.81 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 161.6, 154.4, 144.8, 135.5, 135.4, 128.8, 128.7, 128.6, 115.5, 111.8, 111.6, 86.9, 83.7, 67.6, 55.5, 21.0. HRMS (ESI $^+$) Calc. for $\text{C}_{18}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}^+]$ 281.1178, found: 281.1175. IR (neat): 2205, 1693, 1287, 1239, 1160, 741 cm^{-1} .



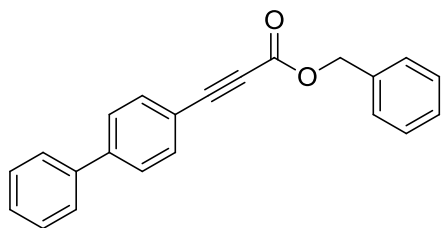
Benzyl 3-(4-chlorophenyl)propiolate (**11**)

Purified by flash column chromatography (ethyl acetate /petroleum ether = 5: 100) to afford **11** as a dark orange crystalline solid (0.1675 g, 62 %). m.p. 65-67 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.52-7.48 (m, 2H), 7.42-7.35 (m, 6H), 7.34-7.33 (m, 1H), 5.26 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ 153.8, 137.3, 135.0, 134.3, 129.2, 128.8, 118.2, 85.5, 81.4, 68.0. HRMS (ESI $^+$) Calc. for $\text{C}_{16}\text{H}_{12}\text{ClO}_2$ $[\text{M}+\text{H}^+]$ 271.0526, found: 271.0530. IR (neat): 2215, 1695, 1287, 1179, 1163, 1086, 823 cm^{-1} .



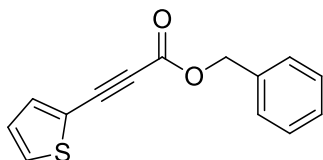
Benzyl 3-(4-bromophenyl)propiolate (**12**)

Purified by flash column chromatography (ethyl acetate /petroleum ether = 5: 100) to afford **12** as a yellow crystalline solid (0.1650 g, 53 %). m.p. 87-89 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.55-7.49 (m, 2H), 7.46-7.33 (m, 7H), 5.26 (s, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 153.9, 134.5, 132.2, 128.9, 128.8, 125.7, 118.7, 85.6, 81.6, 68.0. HRMS (ESI⁺) Calc. for C₁₆H₁₂O₂Br [M+H⁺] 315.0021, found: 315.0010. IR (neat): 2224, 1695, 1288, 1180, 1163, 950, 742 cm⁻¹.



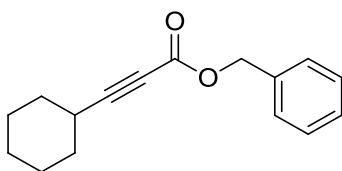
Benzyl 3-([1,1'-biphenyl]-4-yl)propiolate (**13**)

Purified by flash column chromatography (diethyl ether /petroleum ether = 5: 100) to afford **13** as a yellow crystalline solid (0.1595 g, 51 %). m.p. 101-102 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.67-7.63 (m, 2H), 7.62-7.57 (m, 4H), 7.48-7.36 (m, 8H), 5.28 (s, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 154.1, 143.7, 140.0, 135.1, 133.7, 129.2, 128.8, 128.3, 127.4, 118.5, 87.0, 81.3, 67.9. HRMS (ESI⁺) Calc. for C₂₂H₁₇O₂ [M+H⁺], 313.1229 found: 313.1221. IR (neat): 2208, 1701, 1288, 838, 755 cm⁻¹.



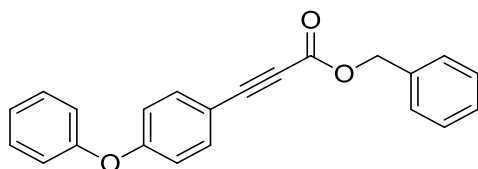
Benzyl 3-(thiophen-3-yl)propiolate (**14**)

Purified by flash column chromatography (ethyl acetate /petroleum ether = 5: 100) to afford **14** as a yellow crystalline solid (0.1050 g, 44 %). m.p. 70-72 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.76-7.73 (dd, J = 3.0, 1.2 Hz, 1H), 7.44-7.35 (m, 5H), 7.32-7.29 (m, 1H), 7.23-7.21 (dd, J = 5.0, 1.2 Hz, 1H), 5.25 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 154.1, 135.1, 134.1, 130.4, 128.9, 128.8, 126.3, 119.0, 82.4, 80.7, 67.9. HRMS (ESI⁺) Calc. for $\text{C}_{14}\text{H}_{11}\text{O}_2\text{S}$ [$\text{M}+\text{H}^+$] 243.0480, found: 243.0518. IR (neat): 2215, 1700, 1260, 1206, 1152, 753 cm^{-1} .



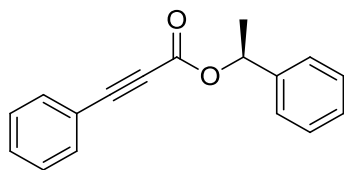
Benzyl 3-cyclohexylpropiolate (**15**)

Purified by flash column chromatography (diethyl ether /petroleum ether = 5: 100) to afford **15** as a pale yellow oil (0.1981 g, 81 %). ^1H NMR (400 MHz, CDCl_3): δ 7.41-7.29 (m, 5H), 5.17 (s, 2H), 2.54-2.44 (m, 1H), 1.87-1.76 (m, 2H), 1.75-1.65 (m, 2H), 1.57-1.42 (m, 3H), 1.38-1.22 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 154.0, 135.3, 128.7, 93.7, 73.0, 69.9, 67.5, 31.6, 29.0, 25.7, 24.8. NMR data is consistent with literature values.⁸ HRMS (ESI⁺) Calc. for $\text{C}_{16}\text{H}_{19}\text{O}_2$ [$\text{M}+\text{H}^+$] 243.1385, found: 243.1390. IR (neat): 2931, 2229, 1706, 1450, 1233, 1085, 989, 749 cm^{-1} .



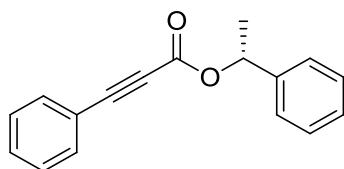
Benzyl 3-(4-phenoxyphenyl)propiolate (**16**)

Purified by flash column chromatography (ethyl acetate /petroleum ether = 4: 100) to afford **16** as a yellow oil (0.1604 g, 49 %). ^1H NMR (400 MHz, CDCl_3): δ 7.55-7.50 (m, 2H), 7.44-7.34 (m, 7H), 7.21-7.15 (m, 1H), 7.08-7.01 (m, 2H), 6.96-6.90 (m, 2H), 5.26 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 160.2, 155.7, 154.2, 135.2, 130.2, 128.8, 124.8, 120.3, 118.1, 113.6, 87.1, 80.4, 67.8. HRMS (ESI $^+$) Calc. for $\text{C}_{22}\text{H}_{17}\text{O}_3$ [$\text{M}+\text{H}^+$] 329.1178, found: 329.1186. IR (neat): 2218, 1704, 1502, 1237, 1177, 692 cm^{-1} .



(*S*)-1-Phenylethyl 3-phenylpropiolate (**17**)*

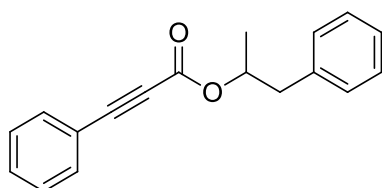
Purified by flash column chromatography (ethyl acetate /petroleum ether = 5: 100) to afford **17** as a golden yellow oil (0.1916 g, 72 %). ^1H NMR (400 MHz, CDCl_3): δ 7.59-7.54 (m, 2H), 7.45-7.28 (m, 8H), 6.05-5.98 (q, J = 6.6 Hz, 1H), 1.65-1.61 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 153.5, 140.8, 133.1, 130.7, 128.4, 126.7, 126.4, 119.8, 86.4, 81.0, 74.5, 22.2. HRMS (ESI $^+$) Calc. for $\text{C}_{17}\text{H}_{15}\text{O}_2$ [$\text{M}+\text{H}^+$] 251.1072, found: 251.1066. IR (neat): 2215, 1702, 1279, 1185, 1170, 1057, 756 cm^{-1} .



(*R*)-1-Phenylethyl 3-phenylpropiolate (18**)***

Purified by column chromatography (ethyl acetate /petroleum ether = 5: 100) to afford **18** as a golden yellow oil (0.1834 g, 73 %). ^1H NMR (400 MHz, CDCl_3): δ 7.60-7.53 (m, 2H), 7.46-7.26 (m, 8H), 6.06-5.98 (q, J = 6.6 Hz, 1H), 1.66-1.59 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ 153.5, 140.8, 133.1, 130.8, 128.8, 128.3, 126.4, 119.8, 86.4, 81.0, 74.5, 22.2. HRMS (ESI⁺) Calc. for $\text{C}_{17}\text{H}_{15}\text{O}_2$ [$\text{M}+\text{H}^+$] 251.1072, found: 251.1076. IR (neat): 2218, 1703, 1279, 1185, 1170, 1057, 756 cm^{-1} .

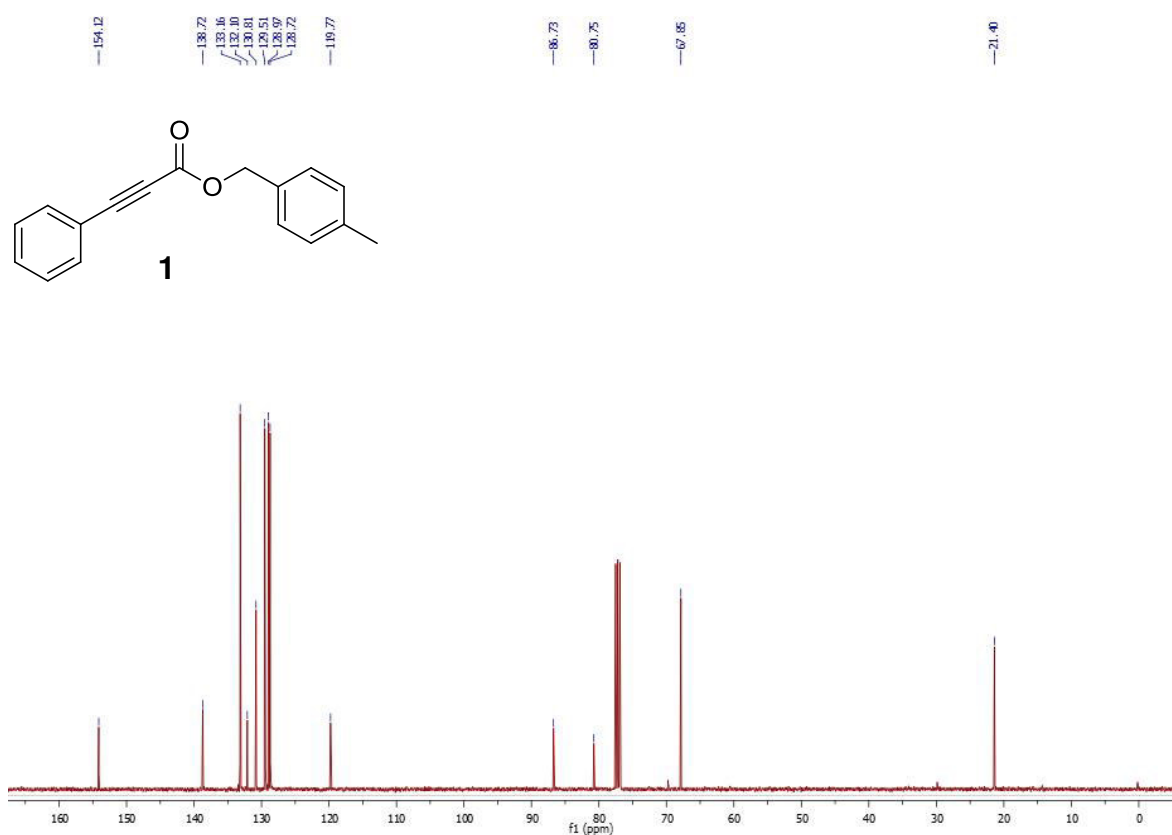
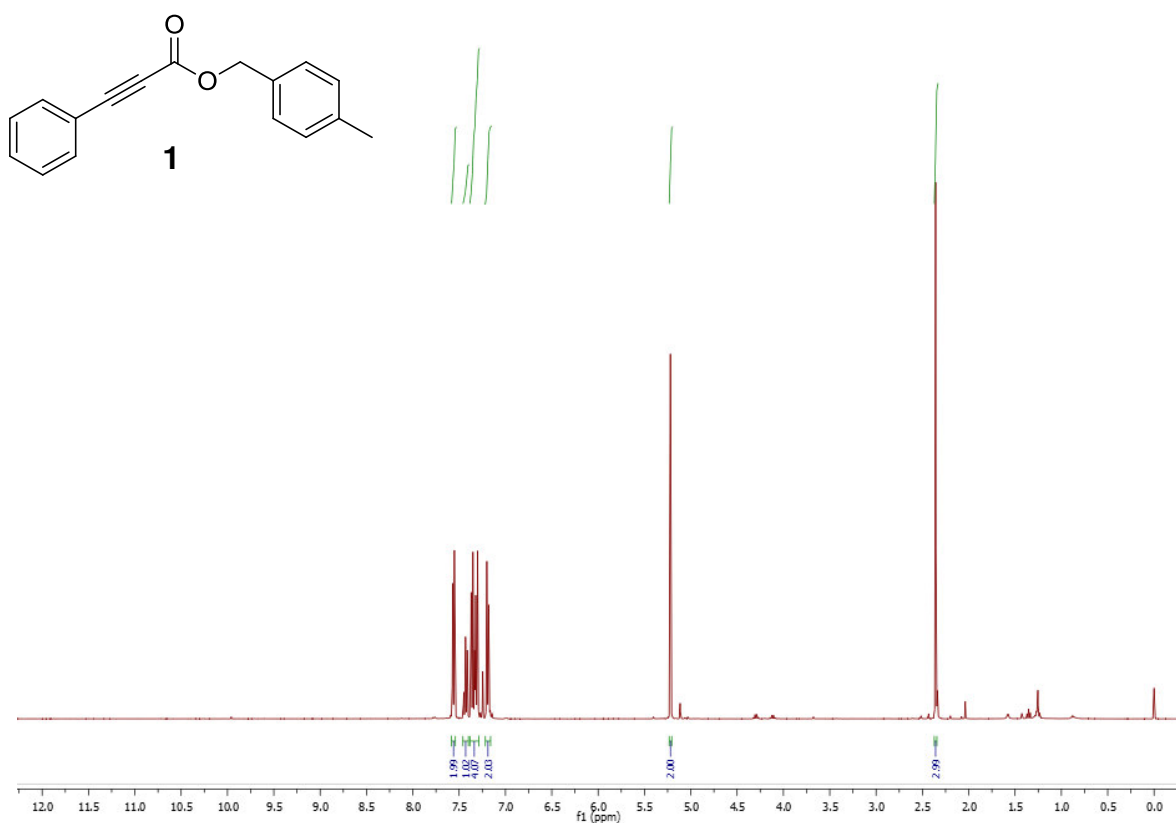
* **17** and **18** were prepared using (*S*)-(-)-1-Phenylethanol and (*R*)-(+)-1-phenylethanol respectively. Chiral HPLC was used to analyse chirality of the products.

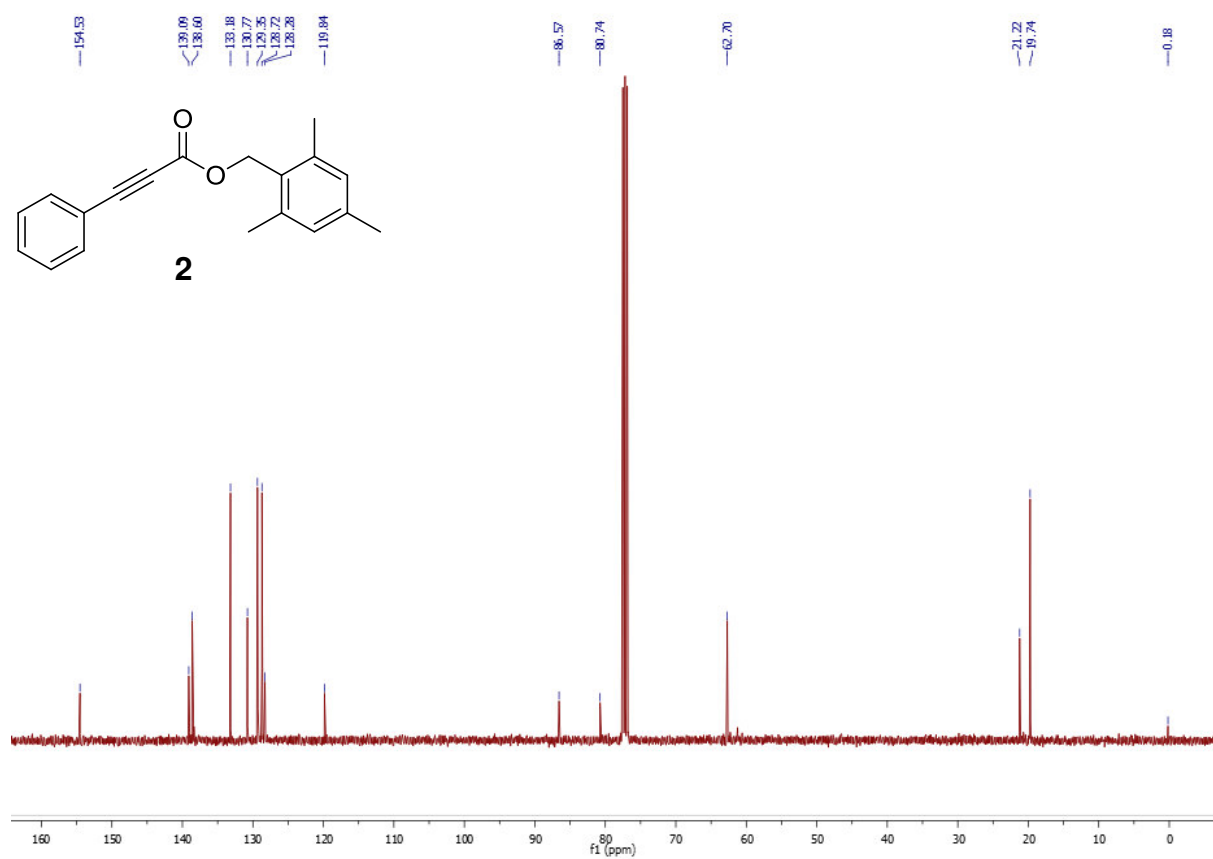
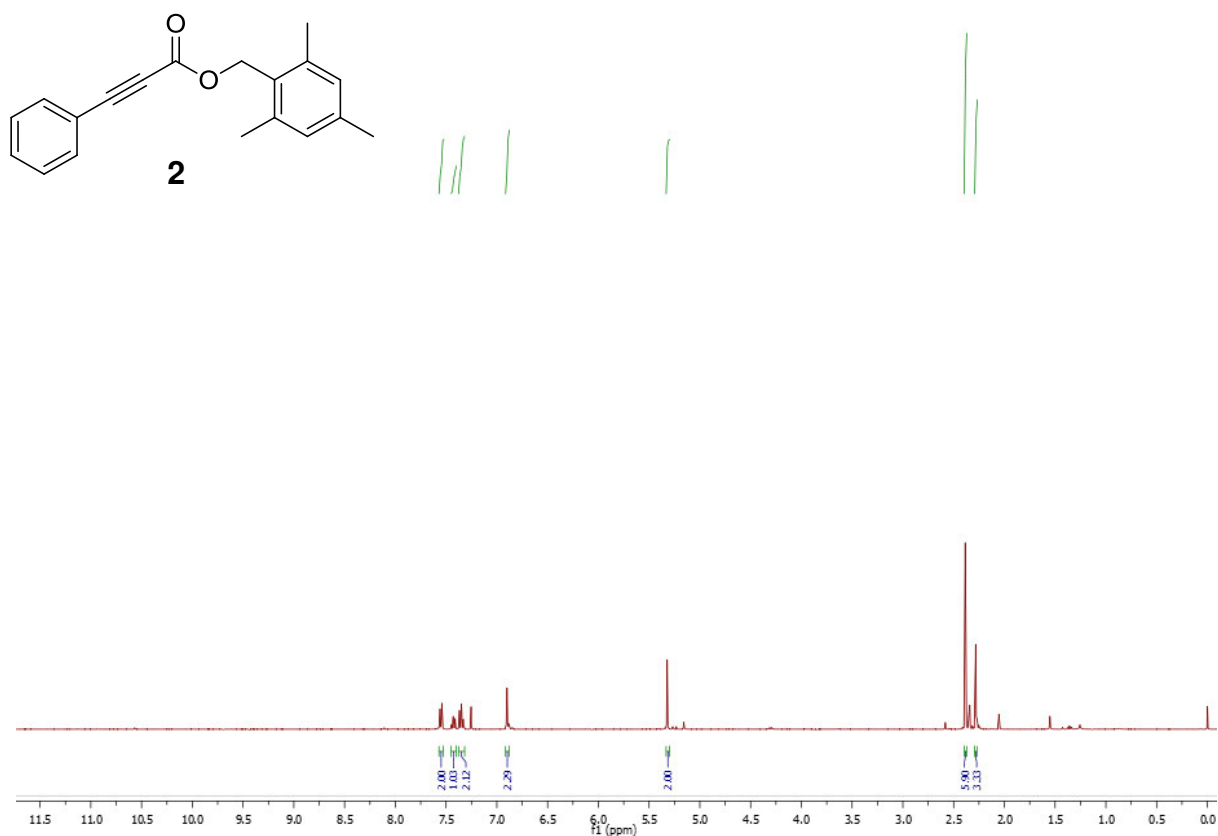


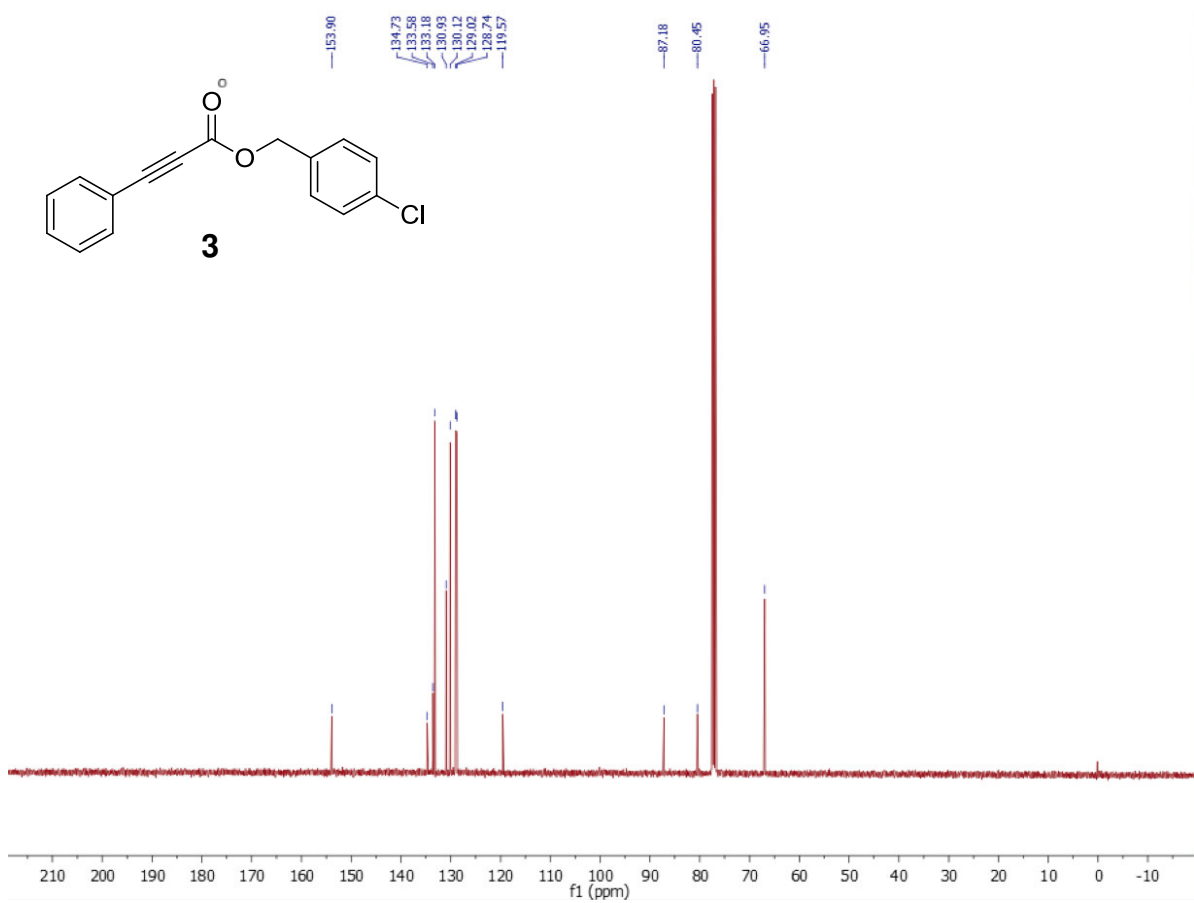
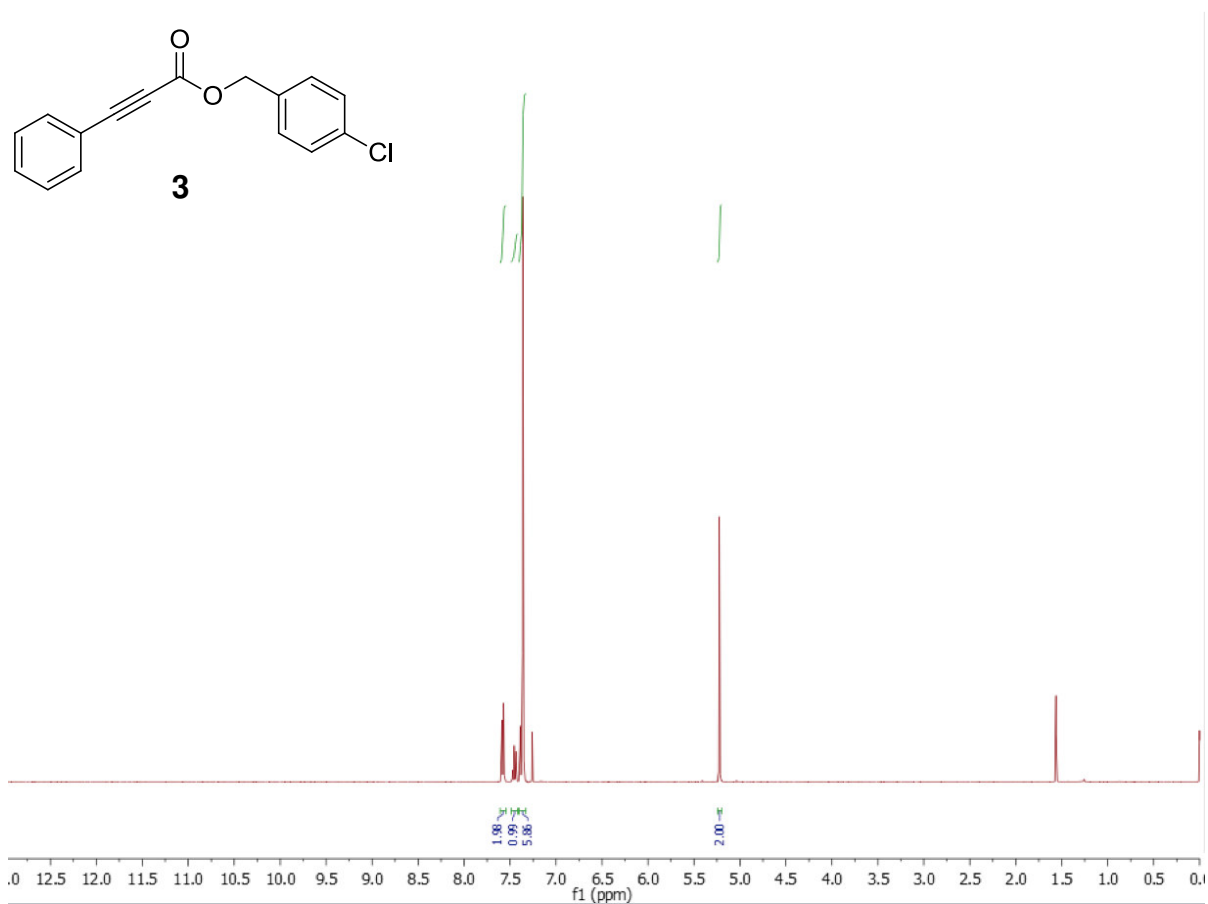
1-Phenylpropan-2-yl 3-phenylpropiolate (19**)**

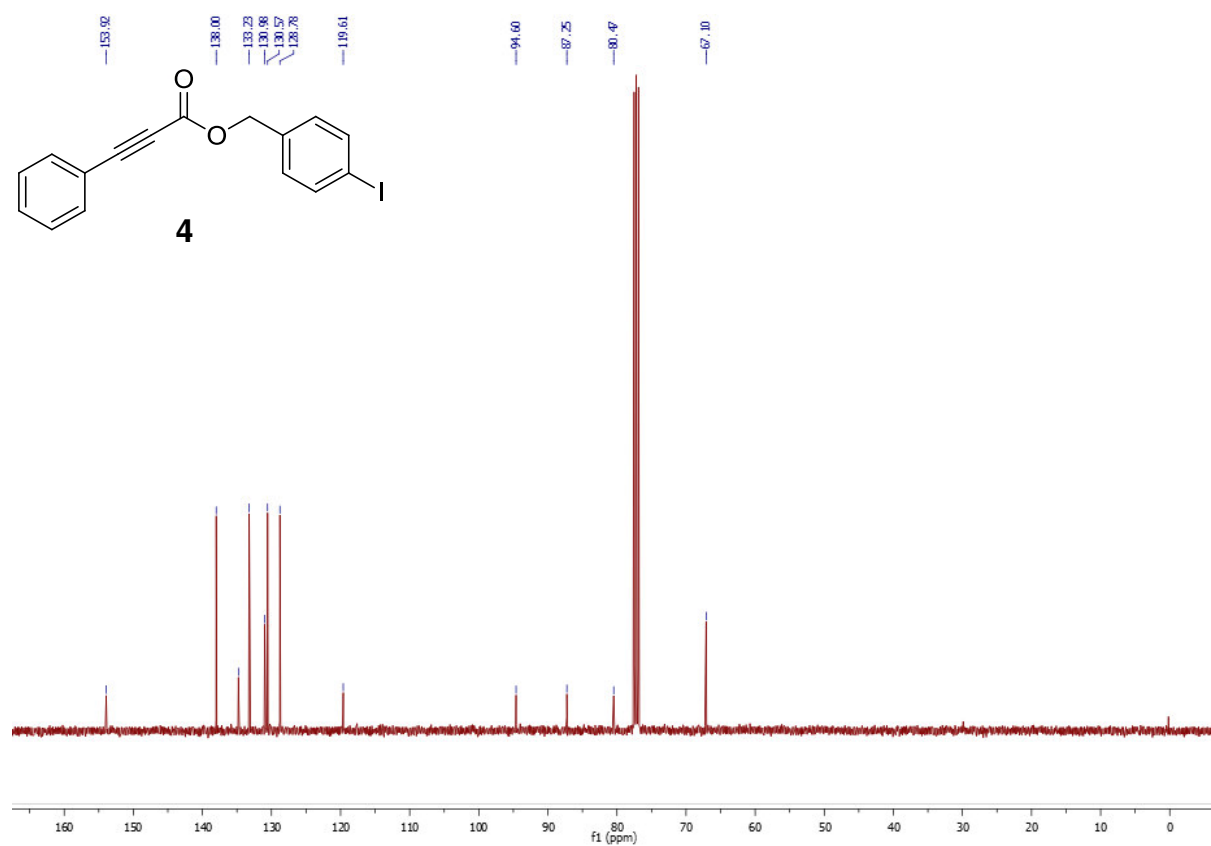
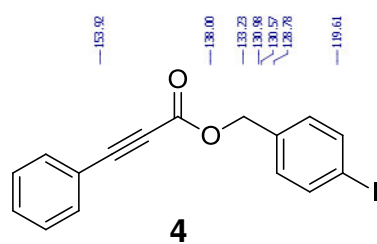
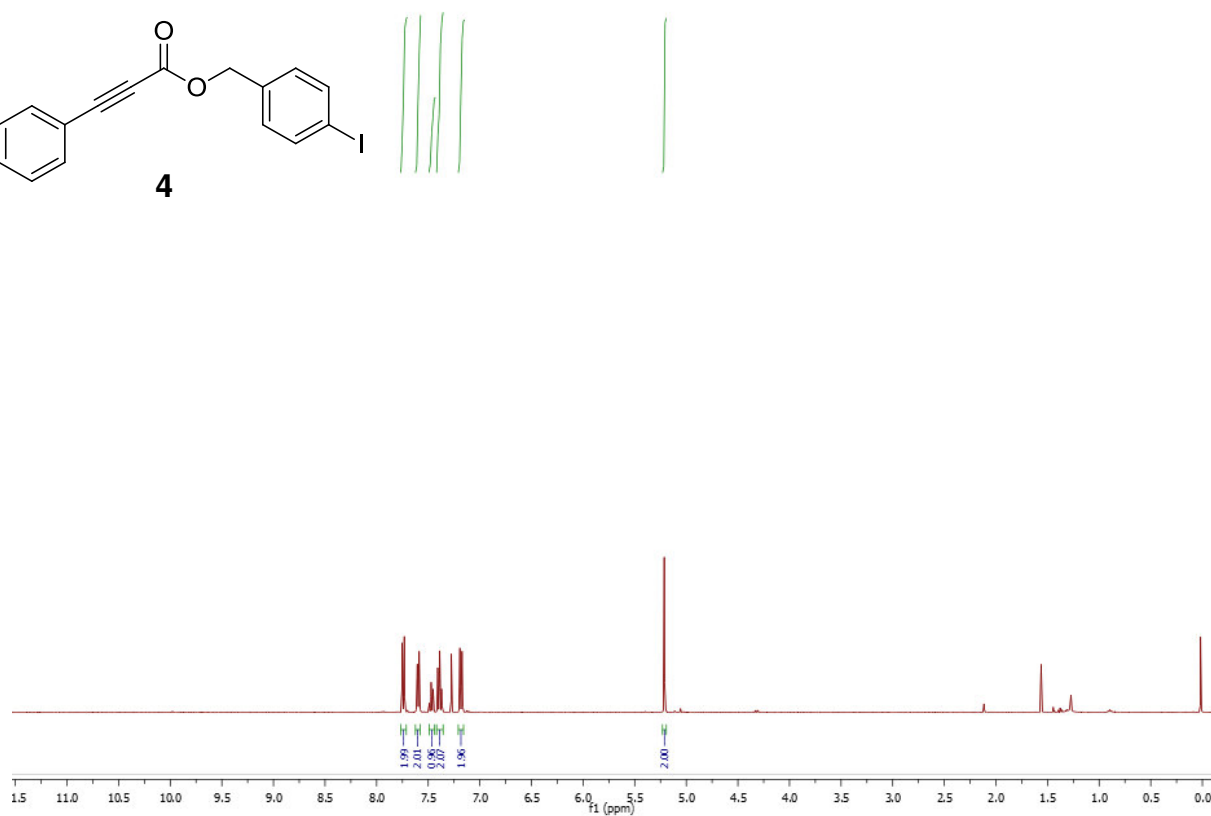
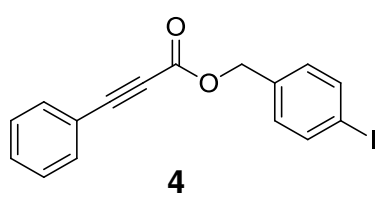
Purified by flash column chromatography (diethyl ether /petroleum ether = 5: 100) to afford **19** as a pale yellow oil (0.2252 g, 85 %). ^1H NMR (400 MHz, CDCl_3): δ 7.61-7.56 (m, 2H), 7.47-7.42 (m, 1H), 7.40-7.34 (m, 2H), 7.34-7.28 (m, 2H), 7.26-7.21 (m, 3H), 5.30-5.21 (dt, J = 13.0, 6.3 Hz, 1H), 3.11-3.00 (dd, J = 13.6, 6.3 Hz, 1H), 2.87-2.78 (dd, J = 13.6, 7.0 Hz, 1H), 1.32-1.28 (d, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 153.8, 137.3, 133.2, 130.7, 129.6, 128.7, 126.9, 119.9, 86.2, 81.1, 73.9, 42.2, 19.4. HRMS (ESI⁺) Calc. for $\text{C}_{18}\text{H}_{16}\text{O}_2\text{Na}$ [$\text{M}+\text{Na}^+$] 287.1048, found: 287.1038. IR (neat): 2218, 1700, 1282, 1206, 1187, 743, 686 cm^{-1} .

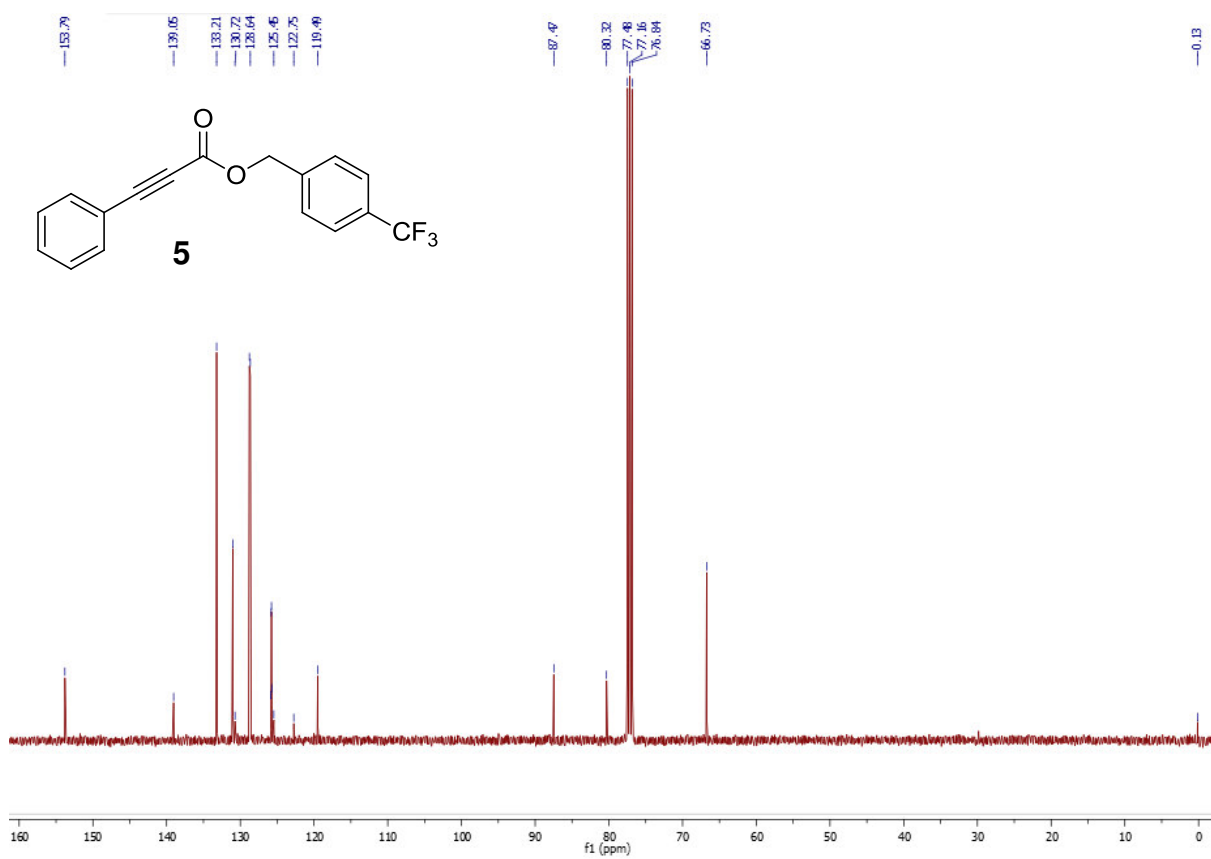
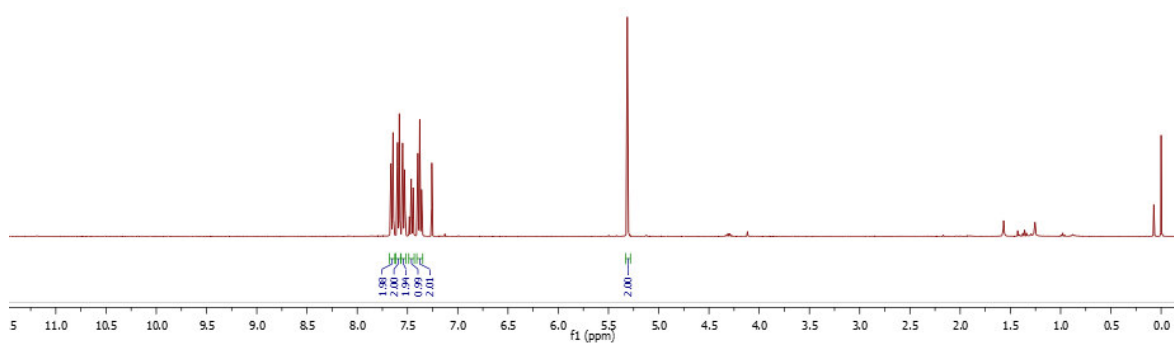
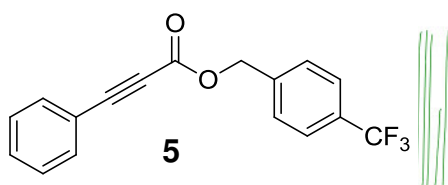
3.5.7 NMR Spectra

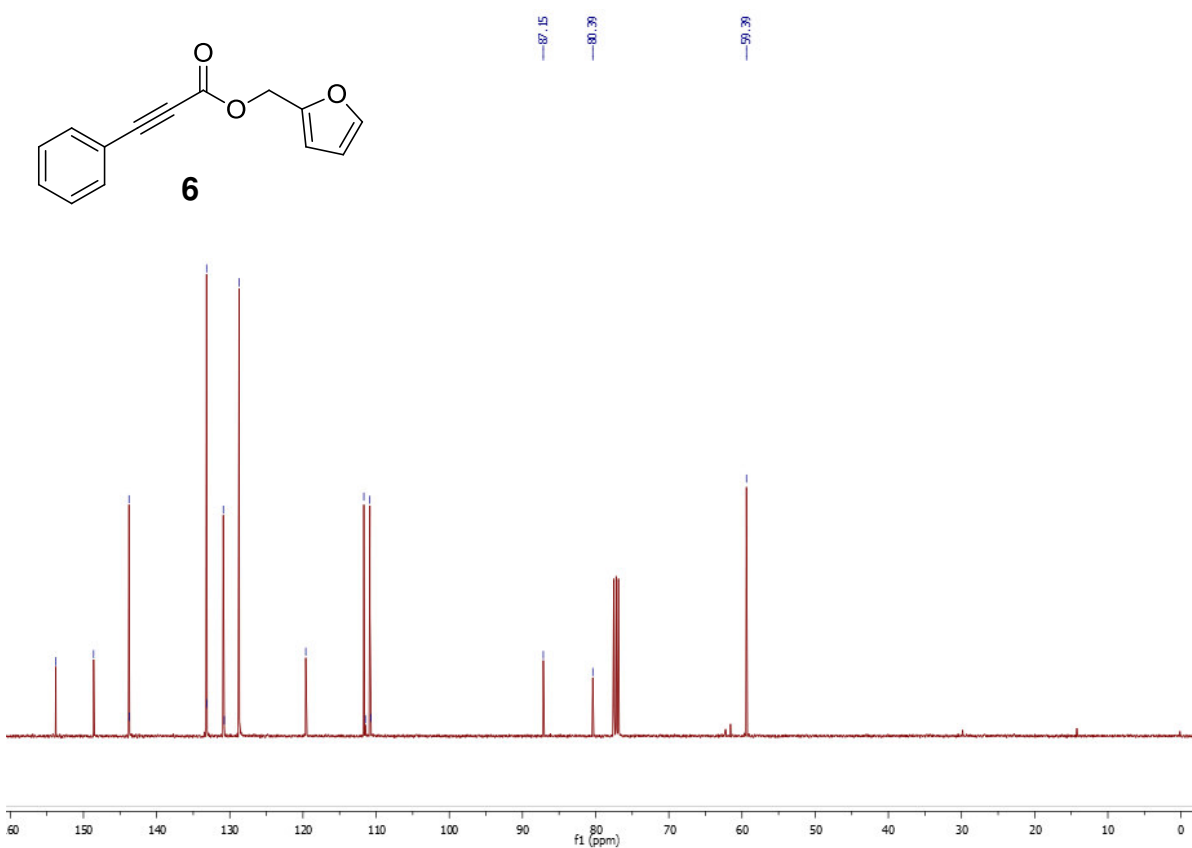
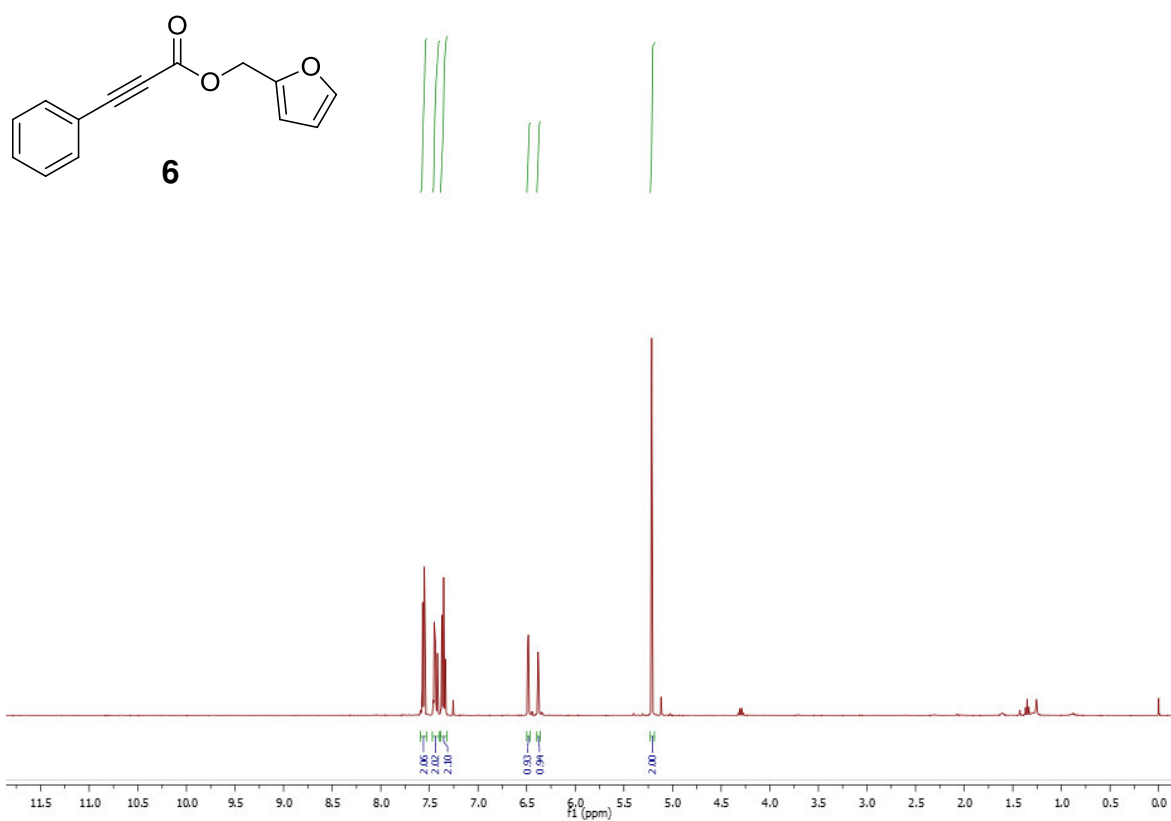


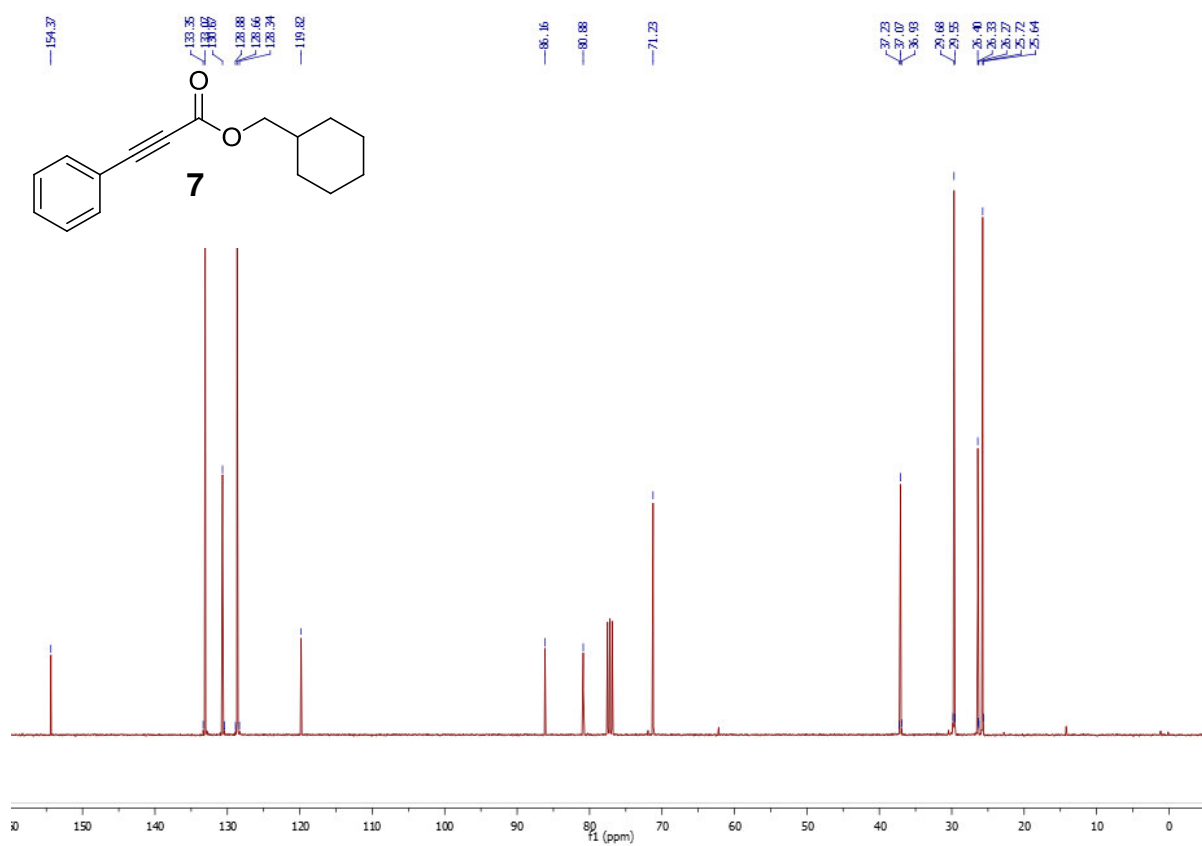
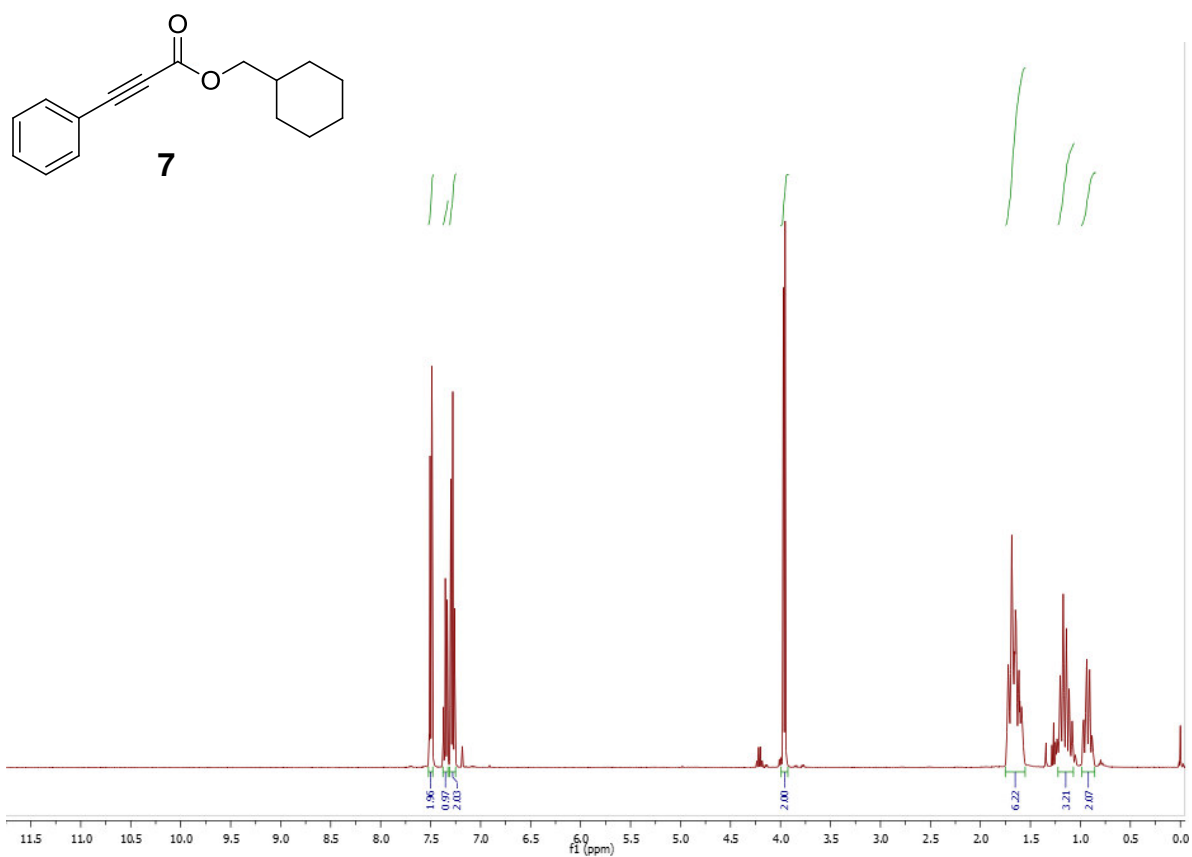


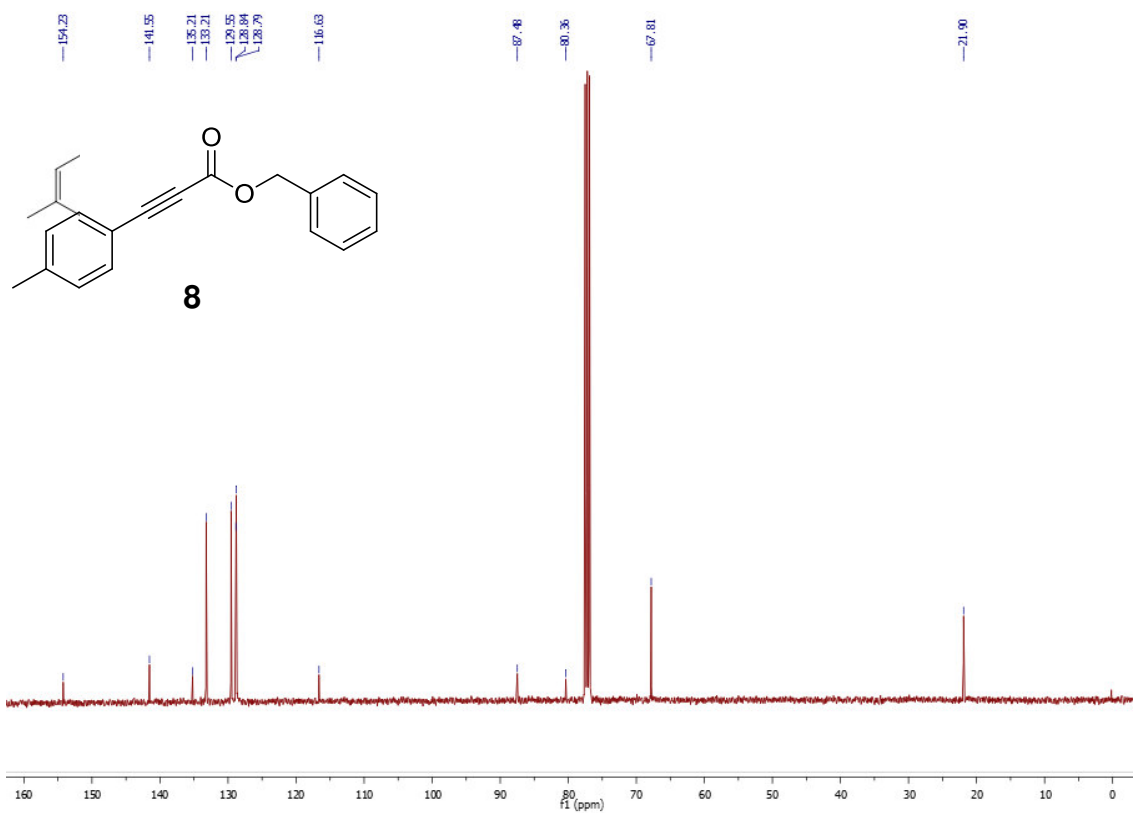
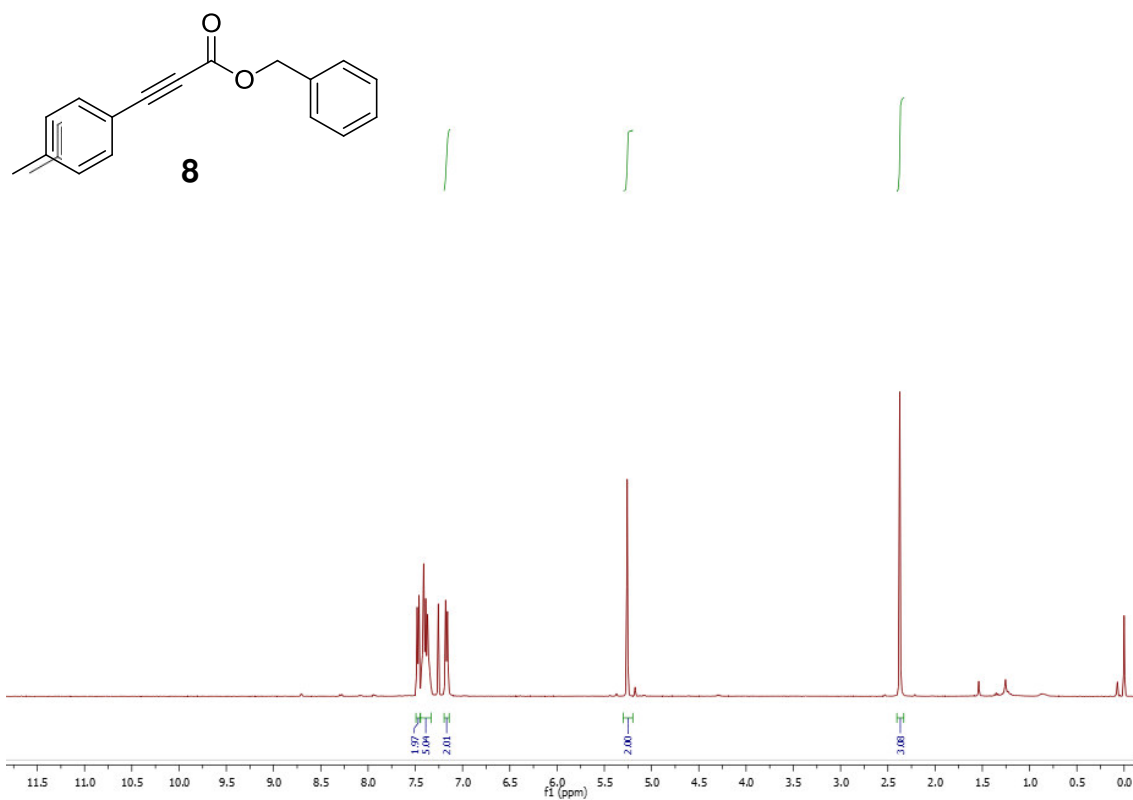


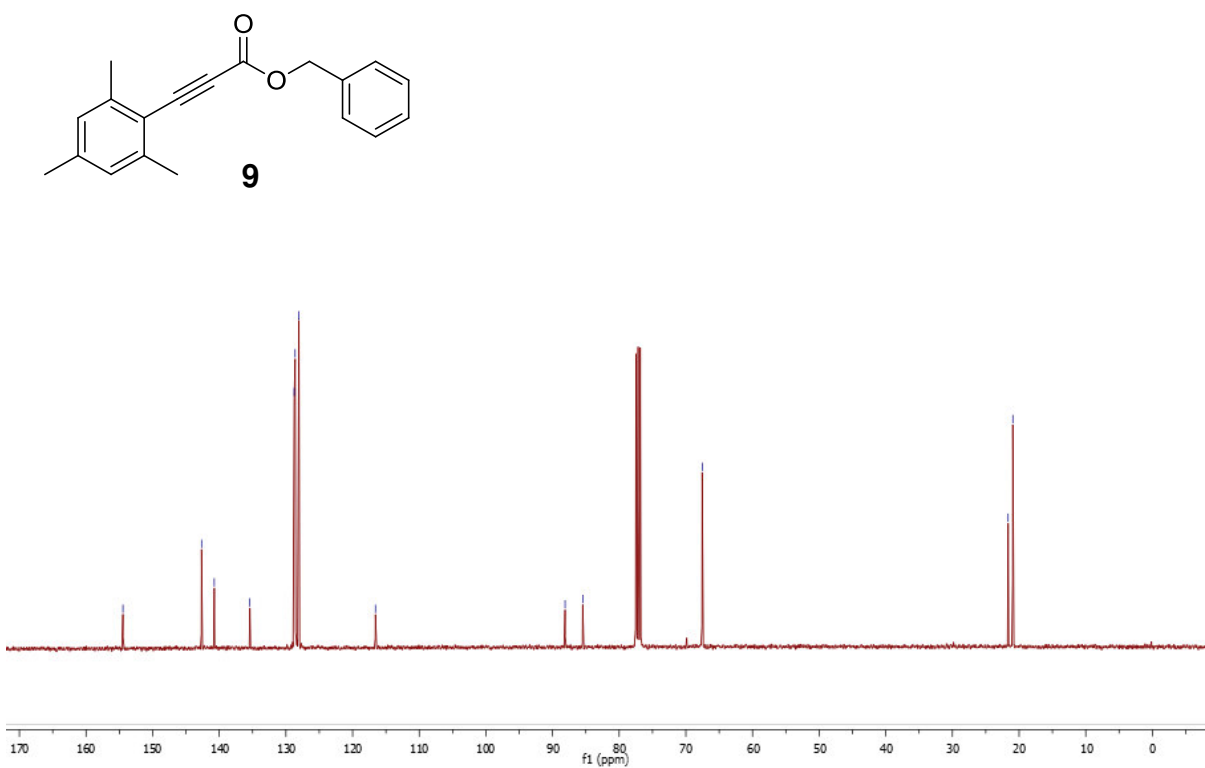
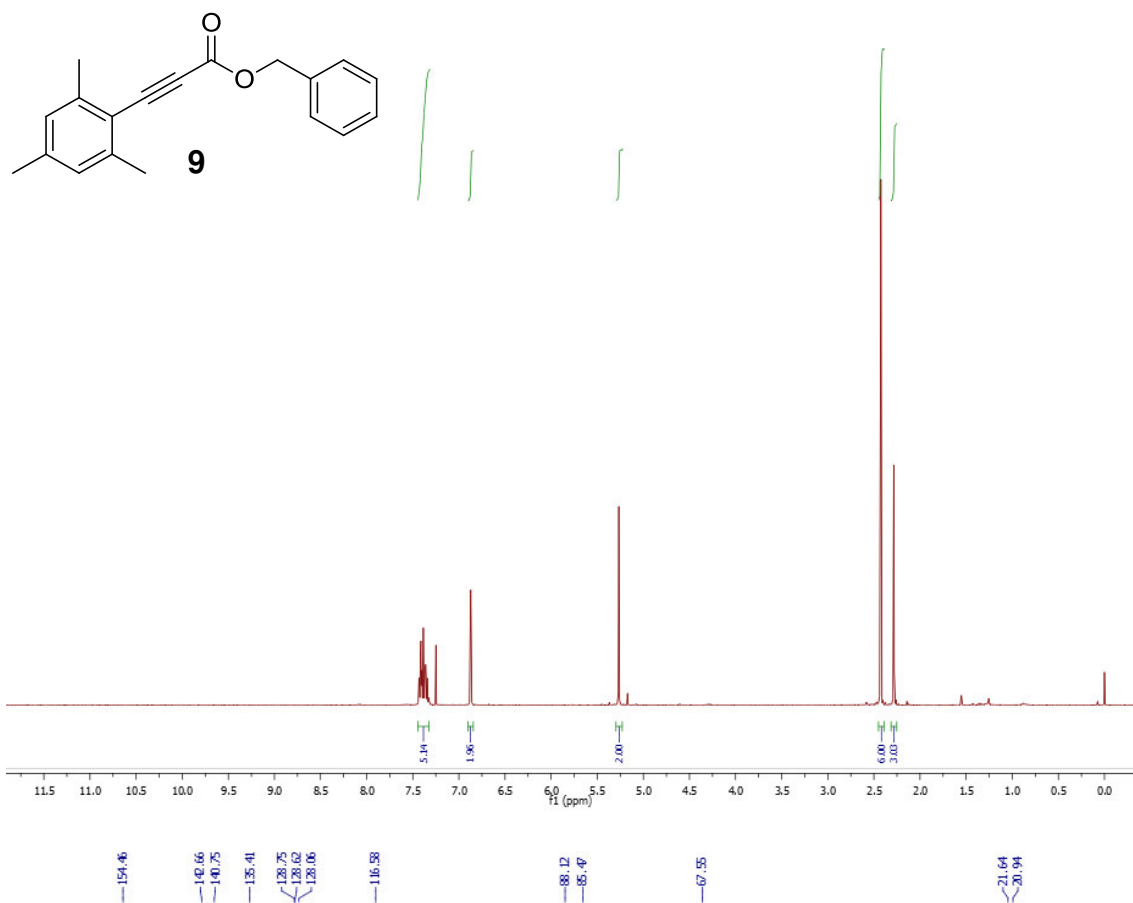


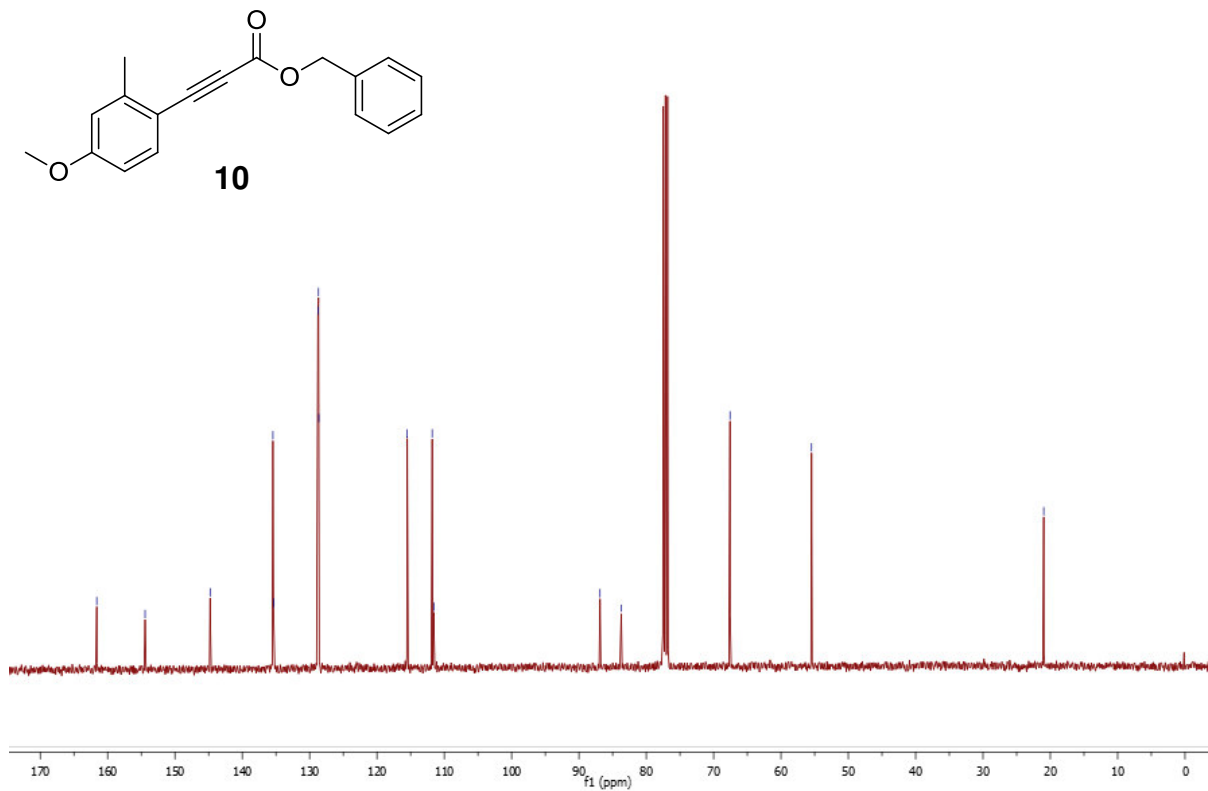
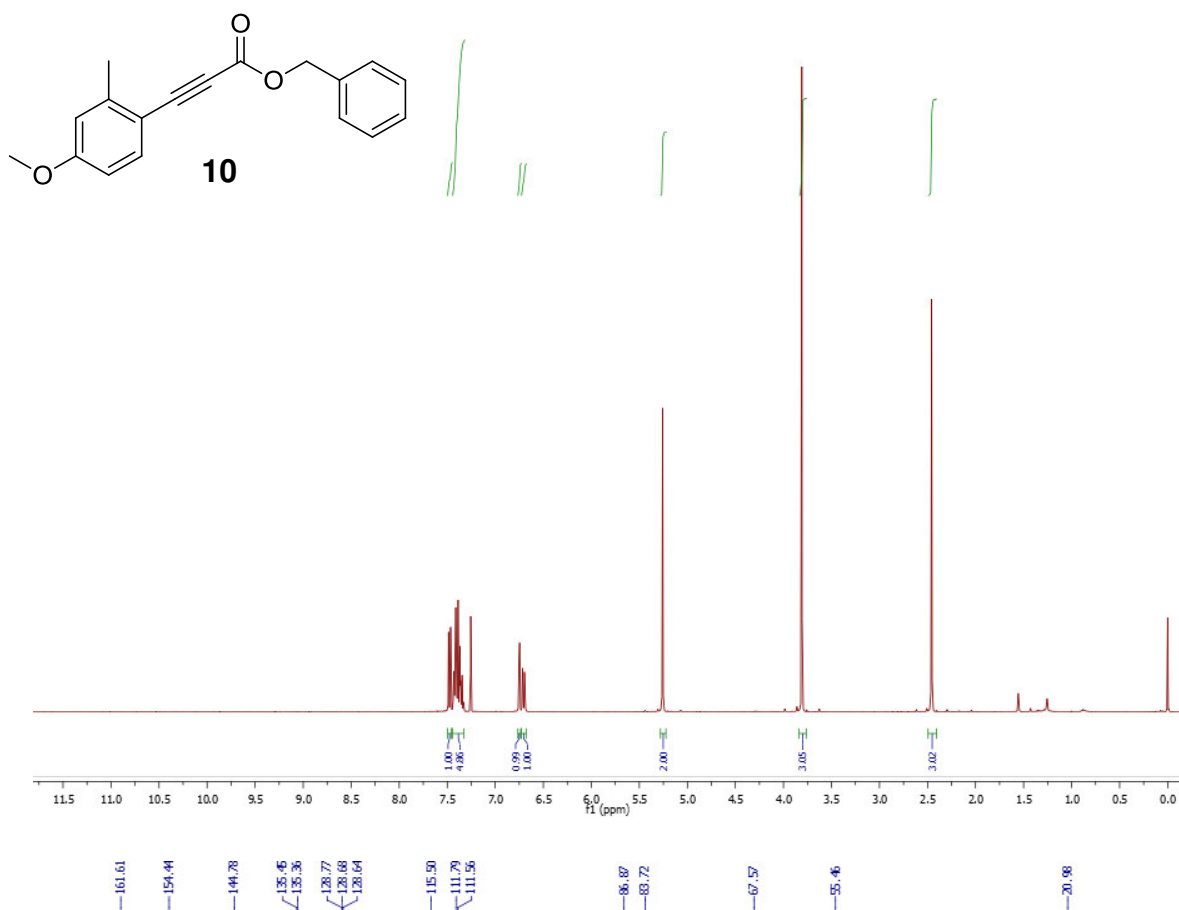


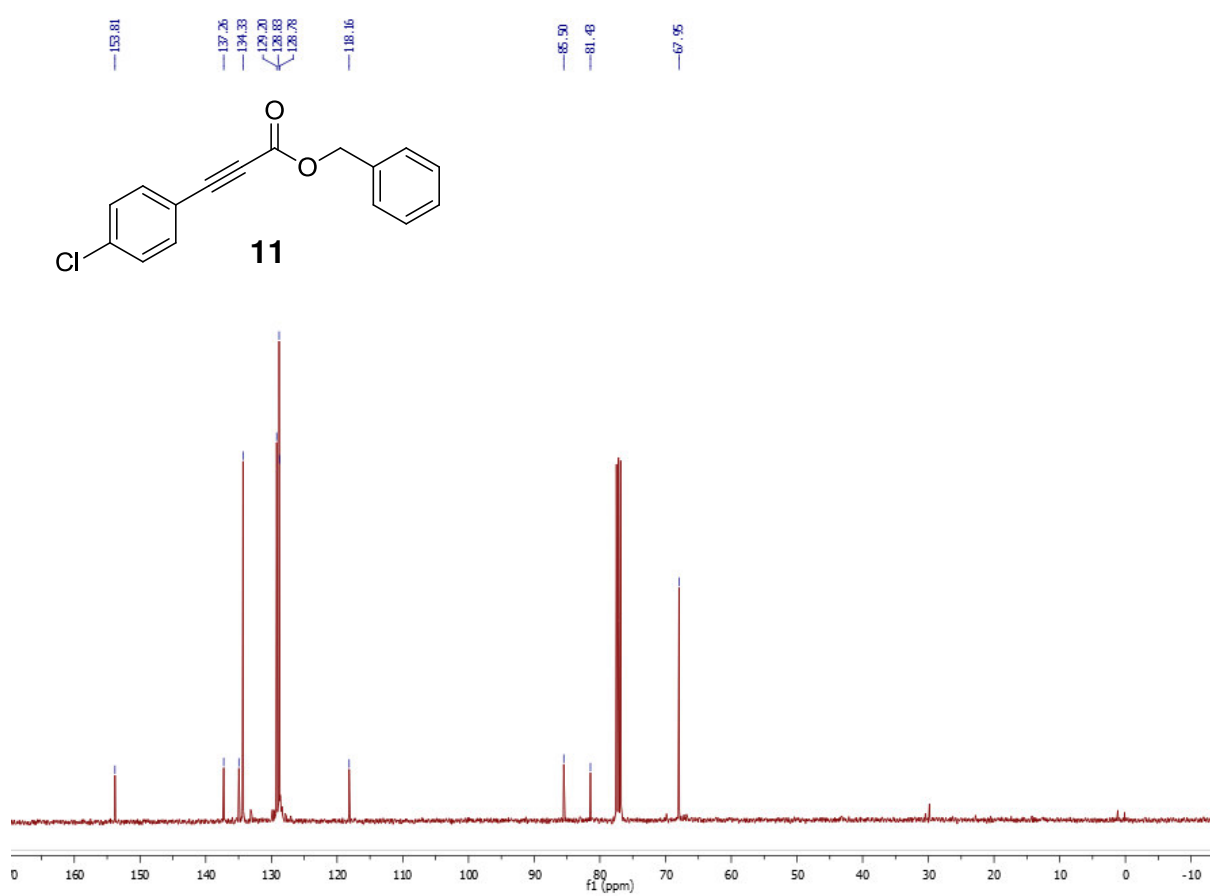
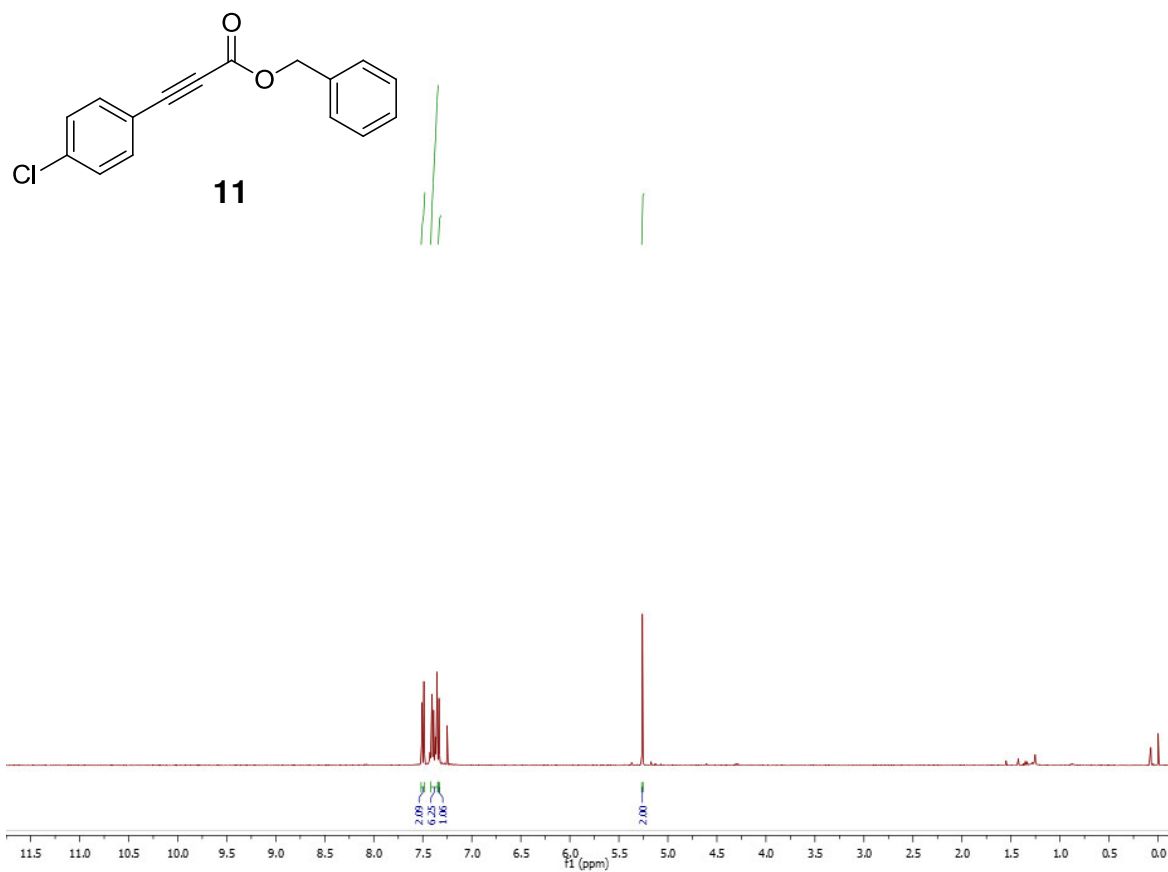


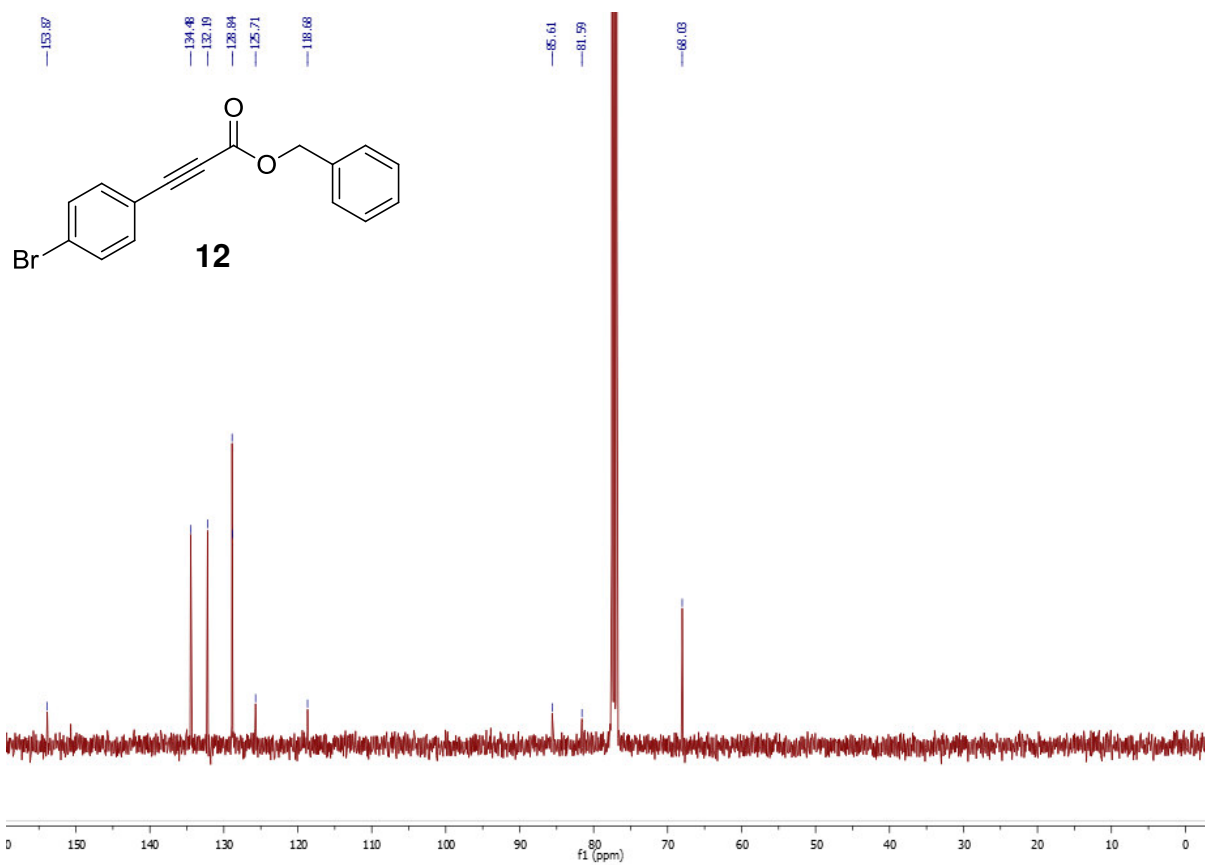
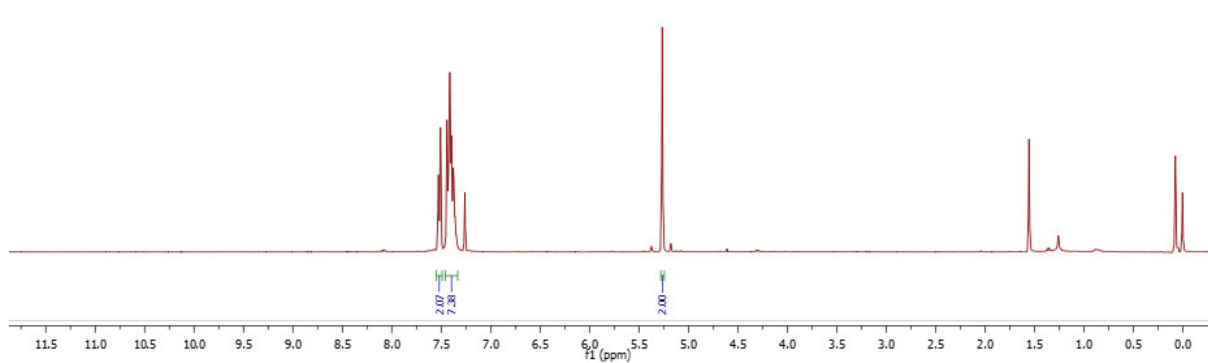
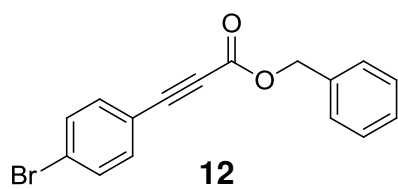


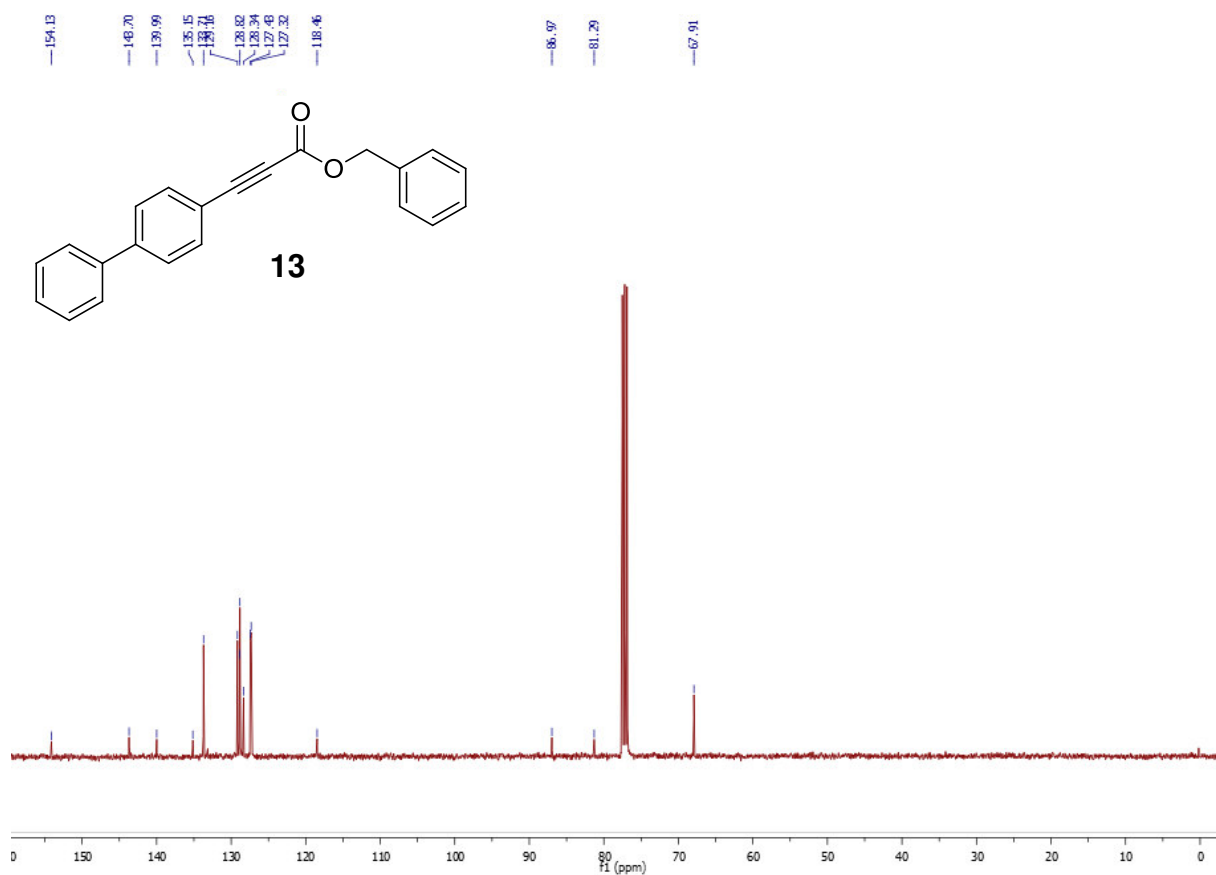
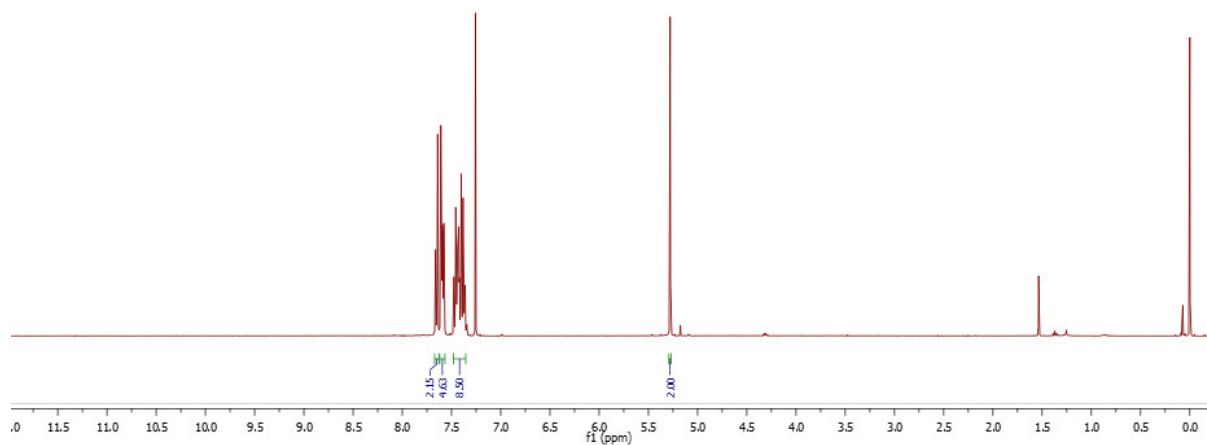
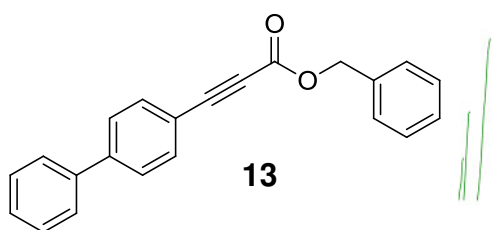


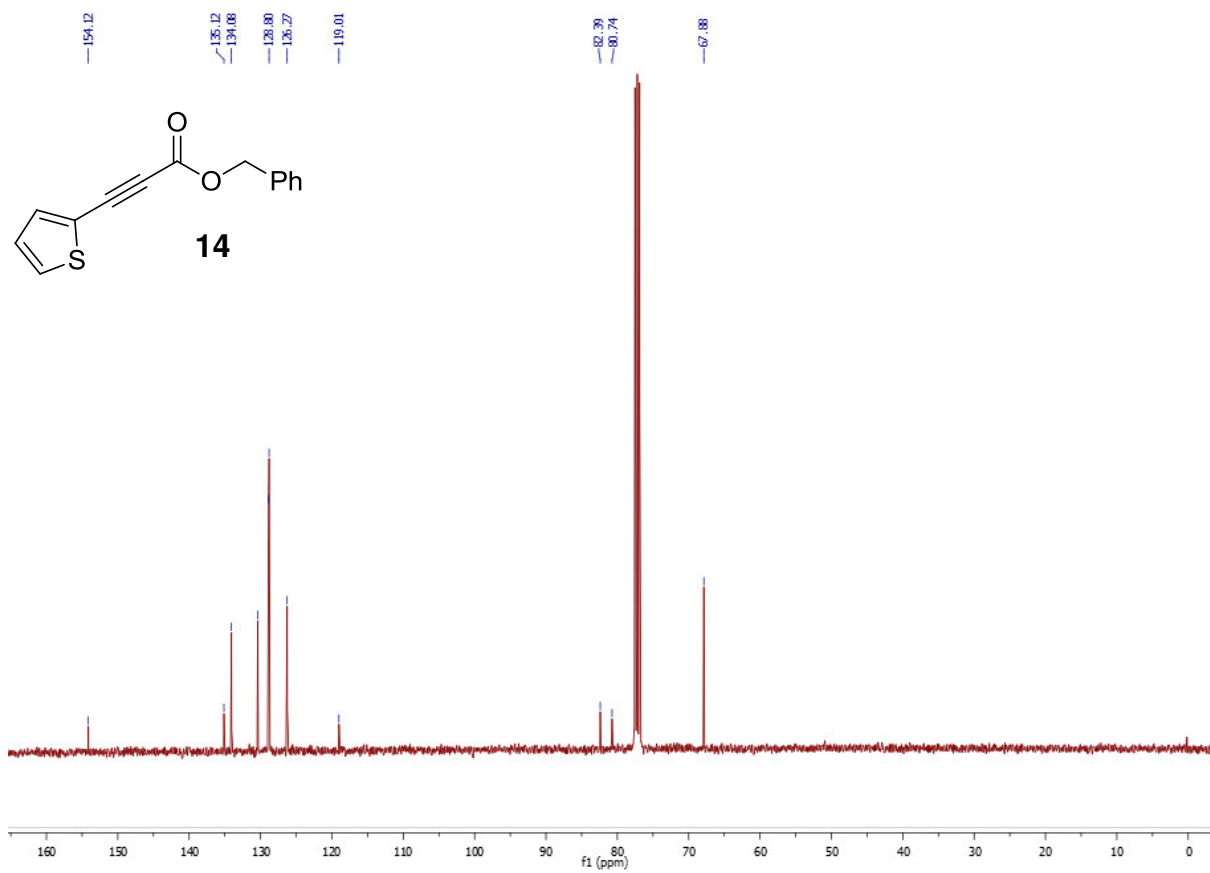
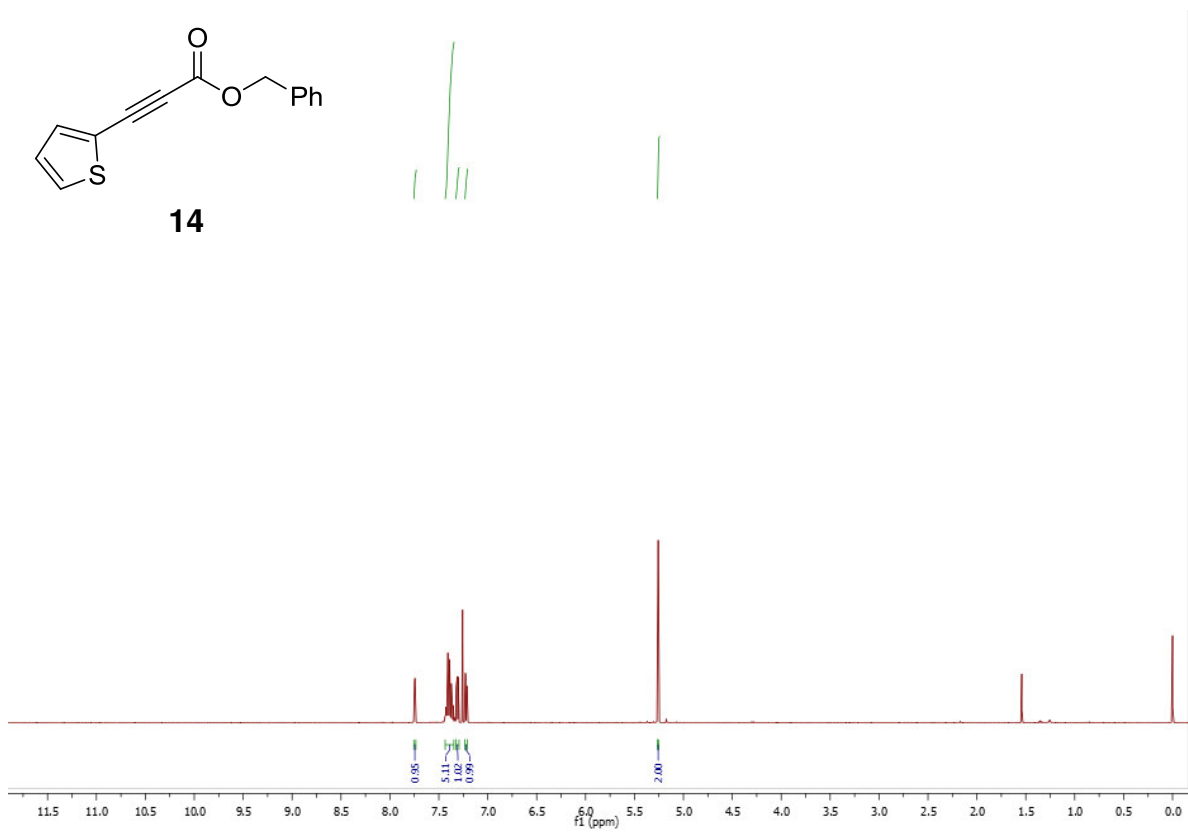


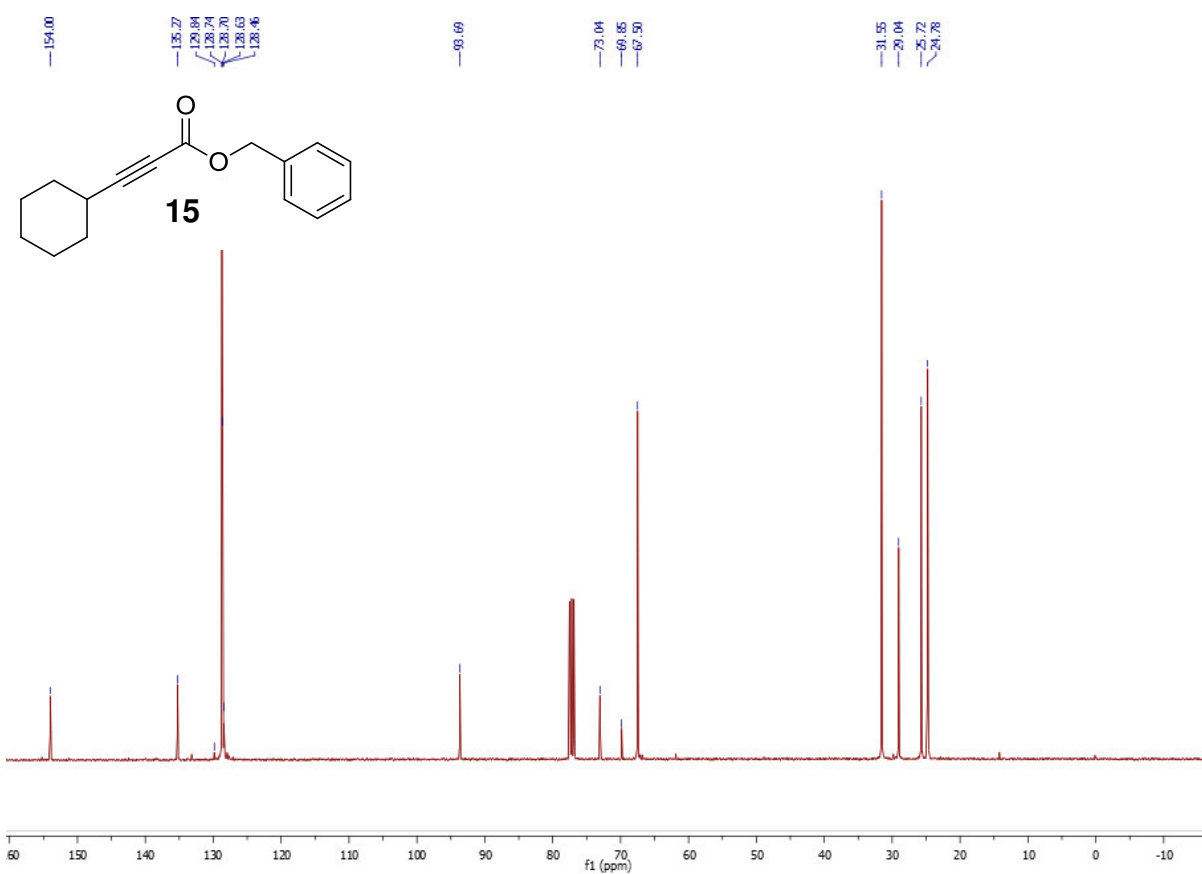
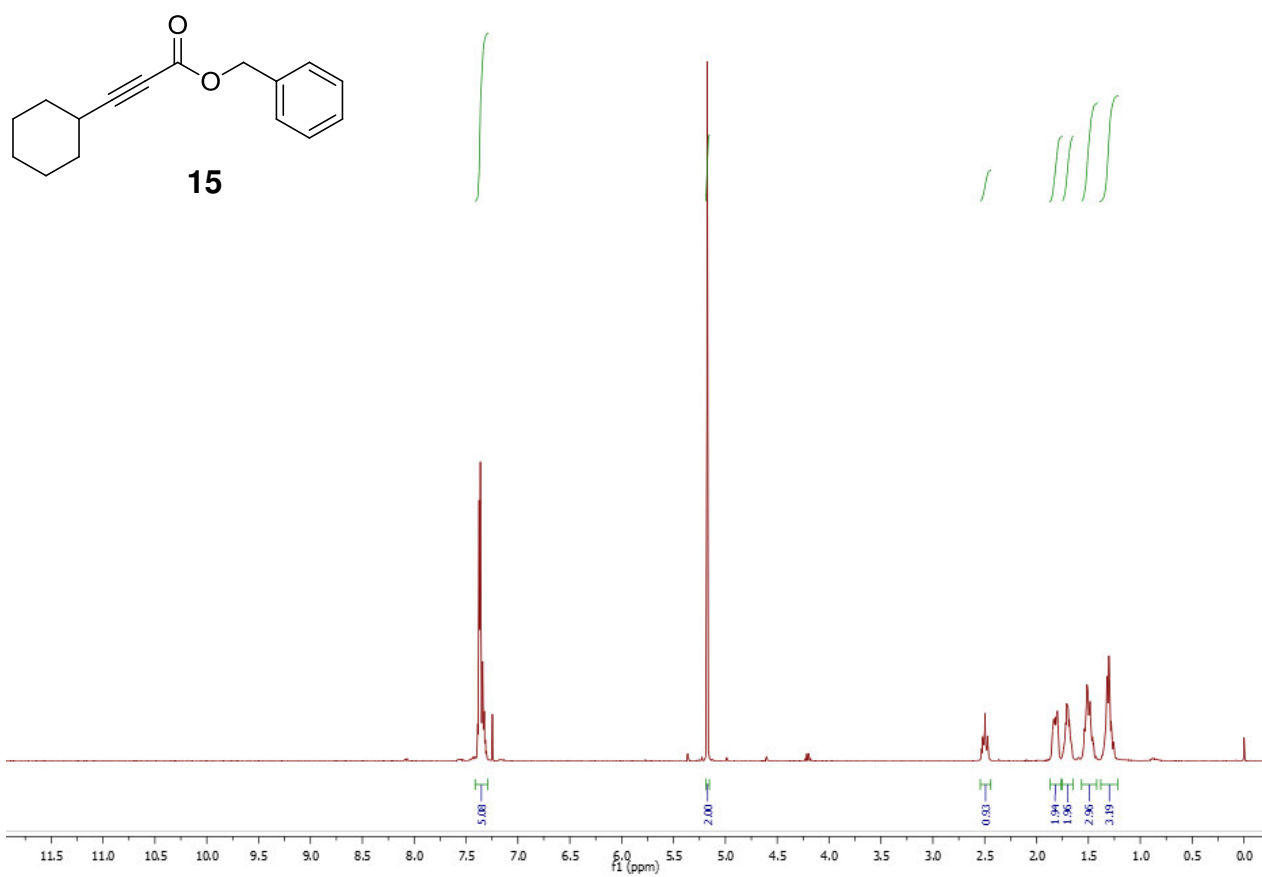


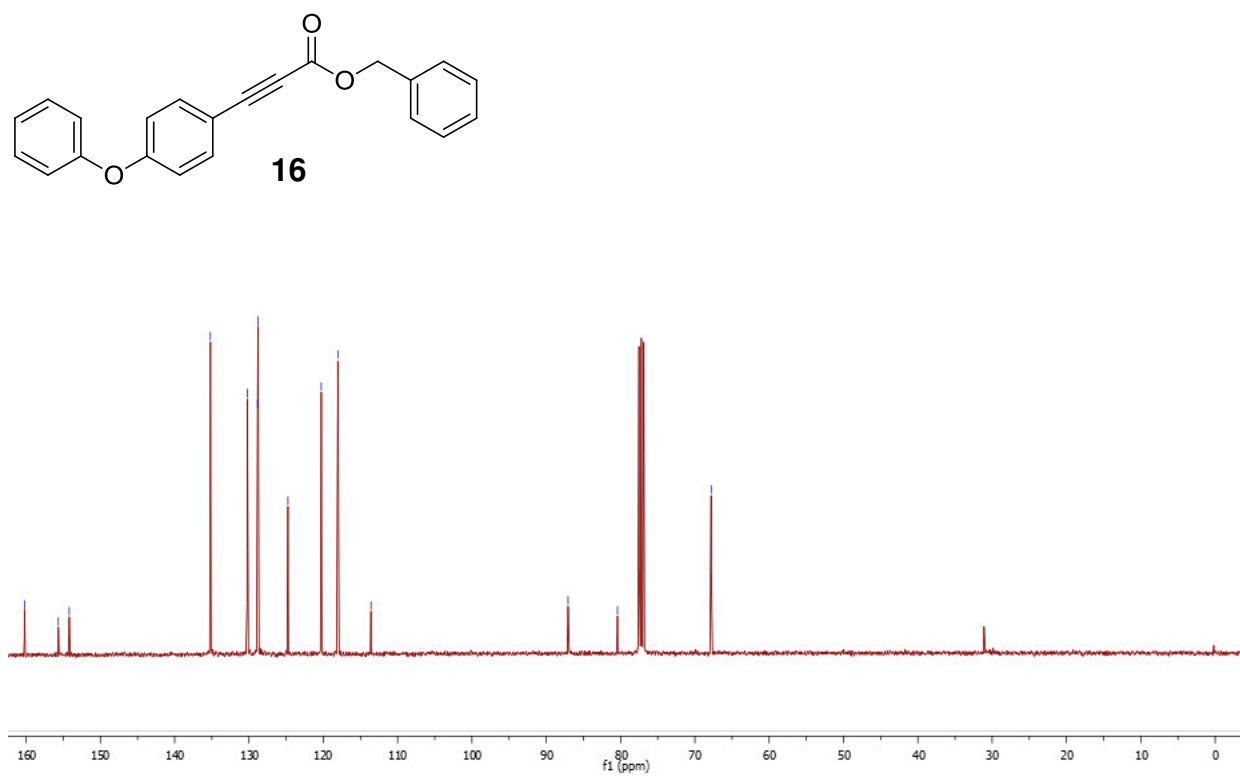
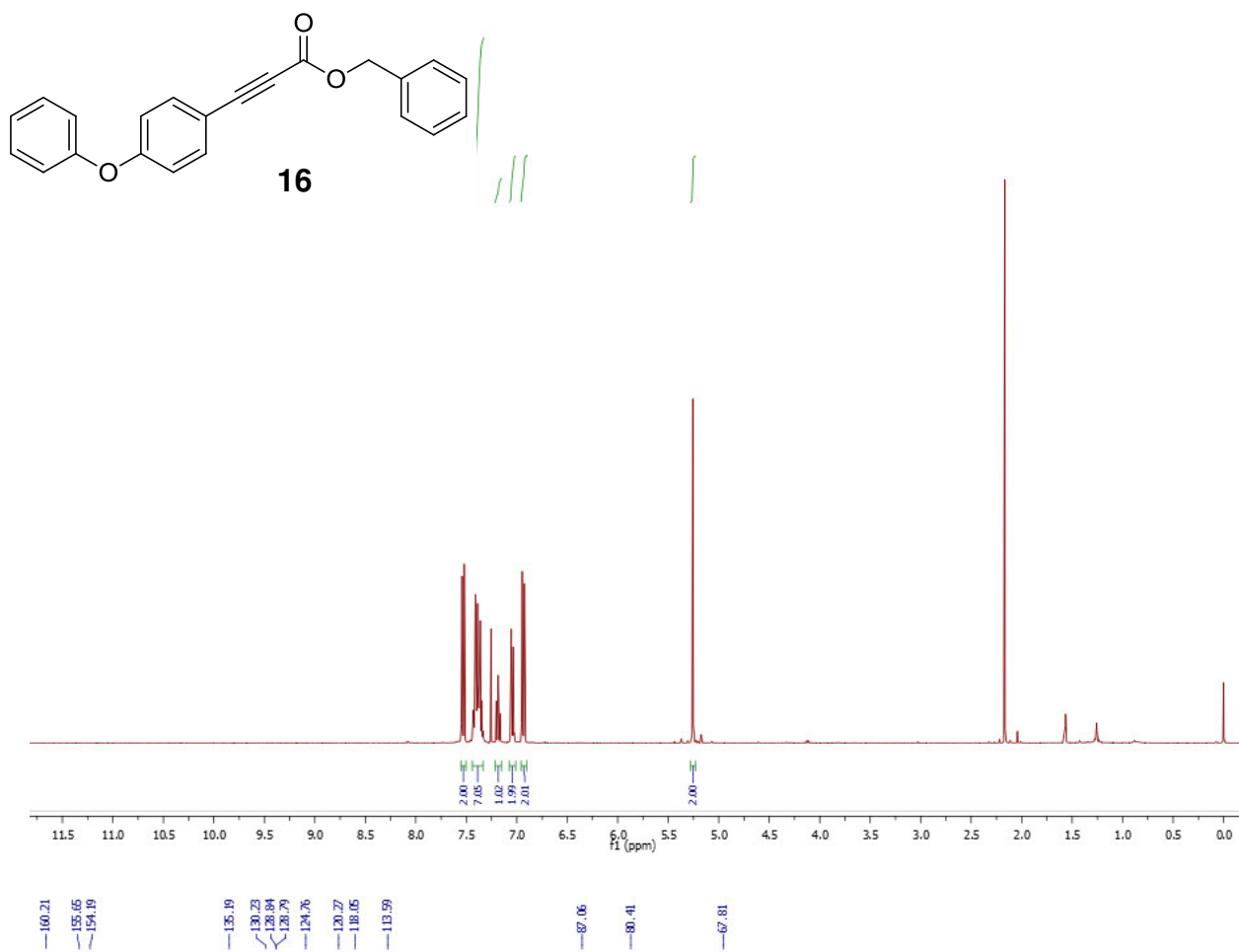


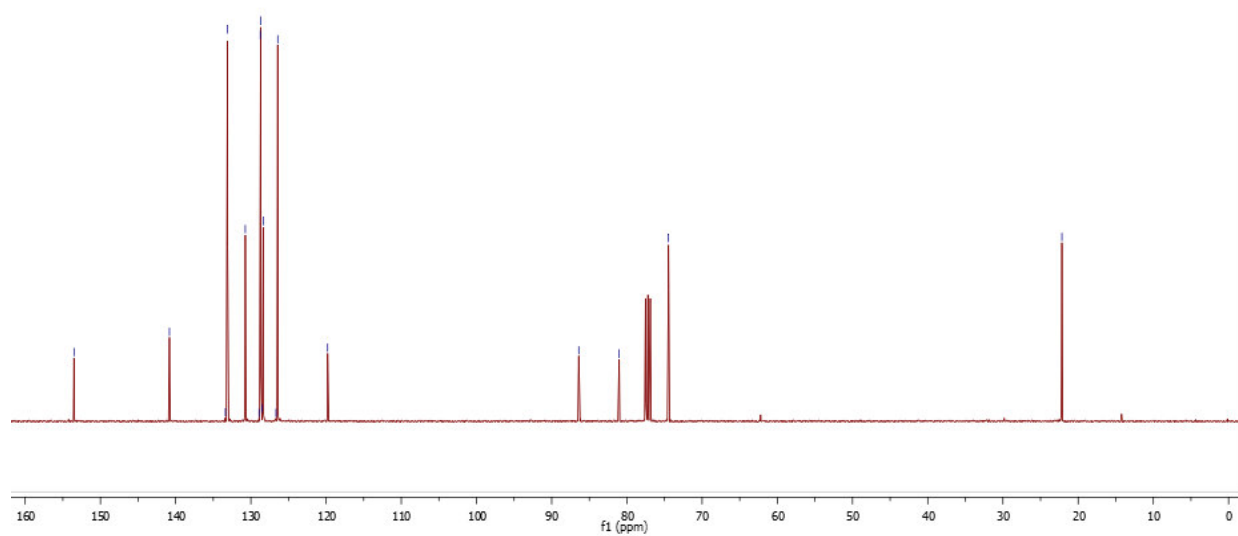
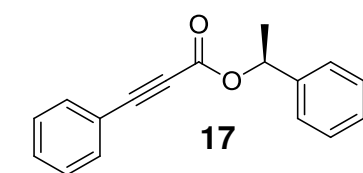
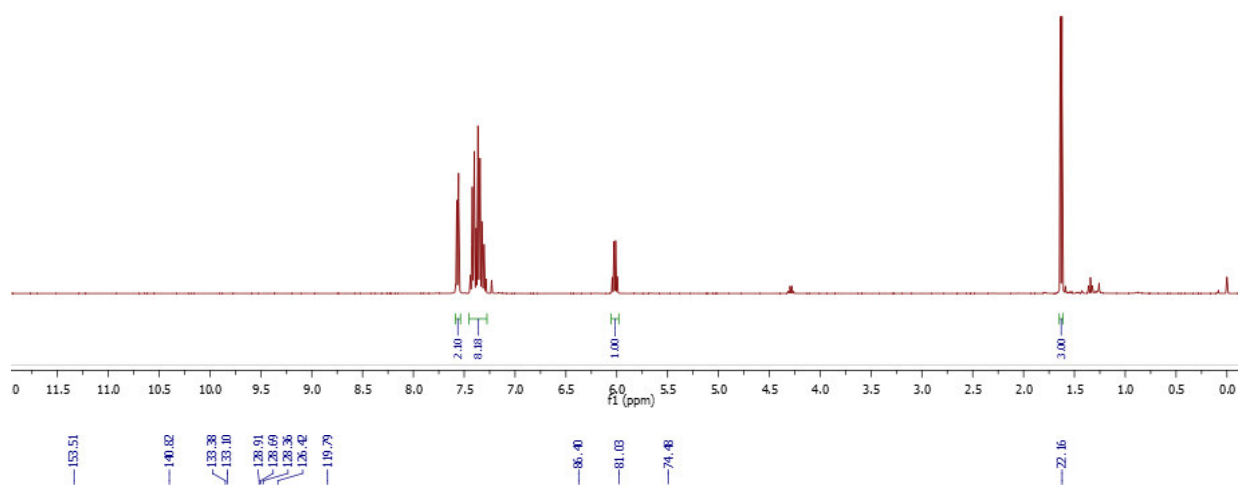
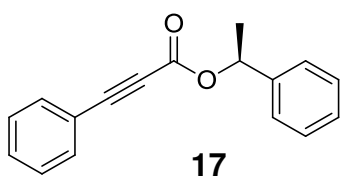


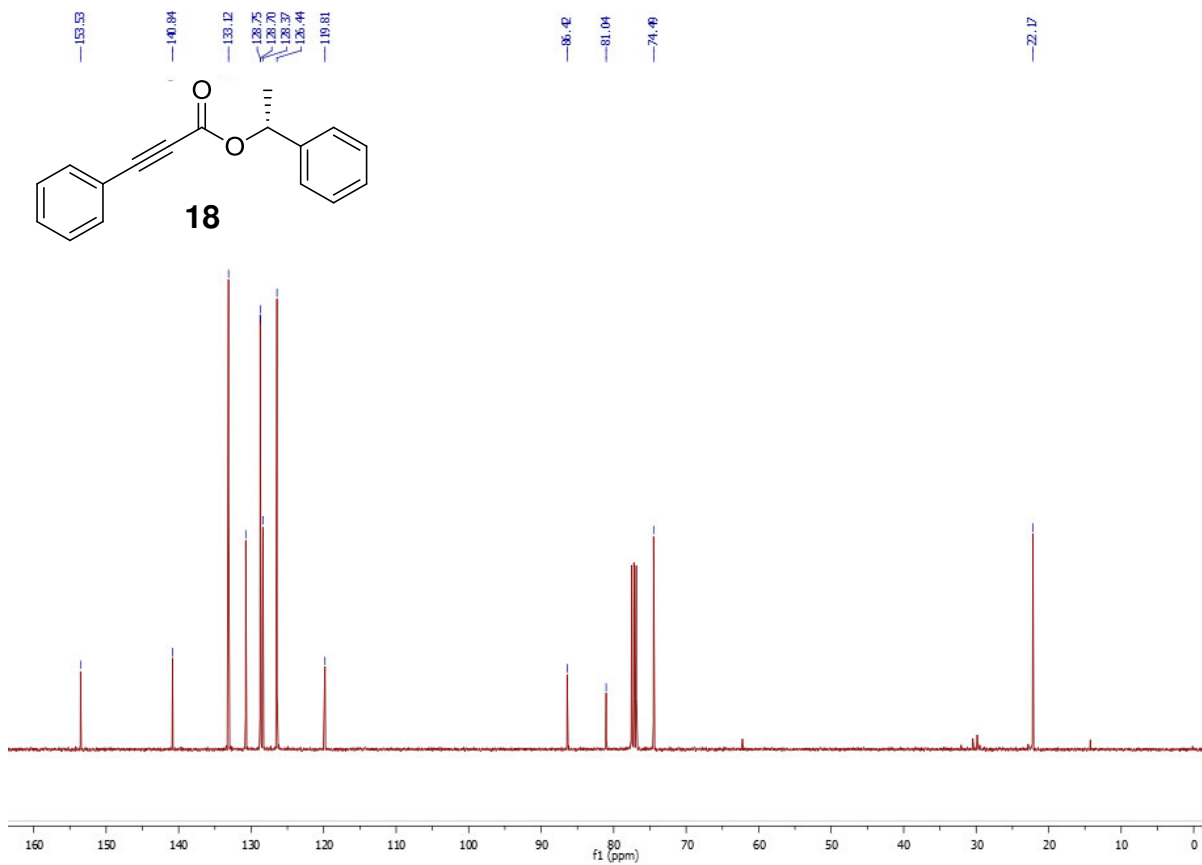
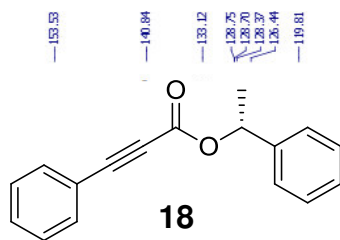
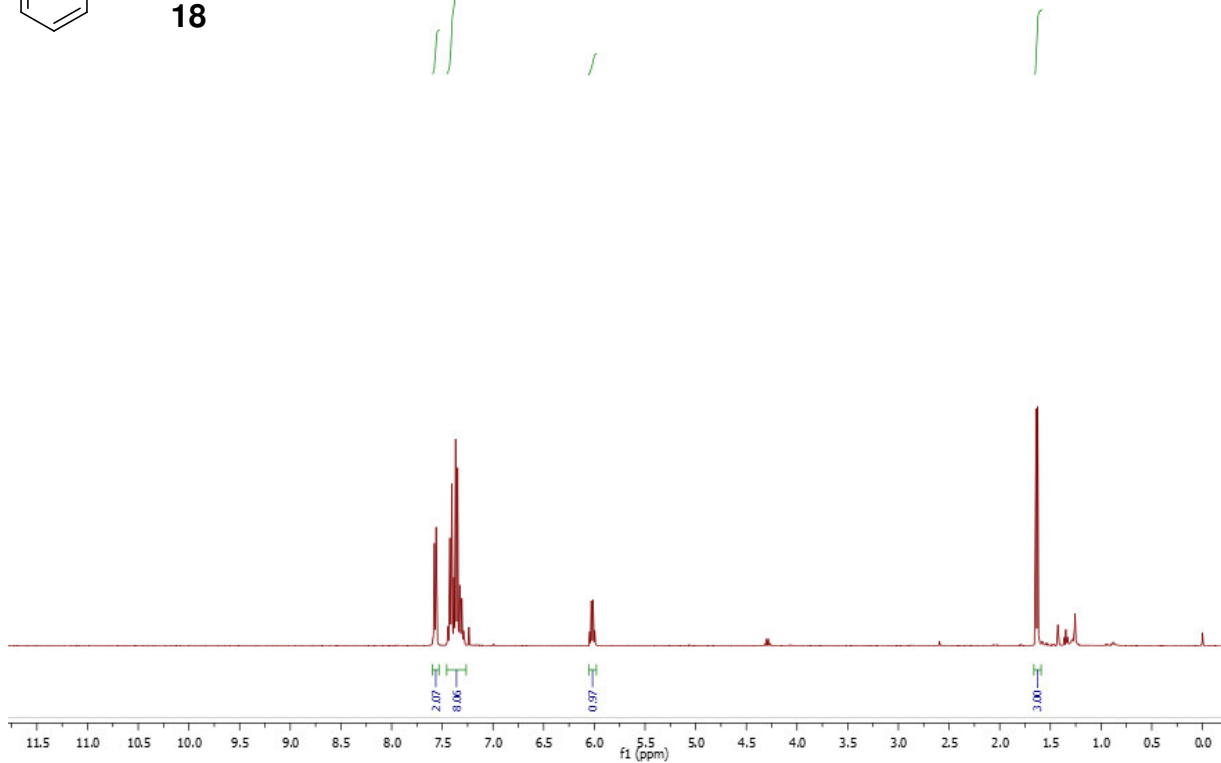
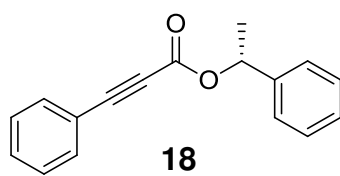


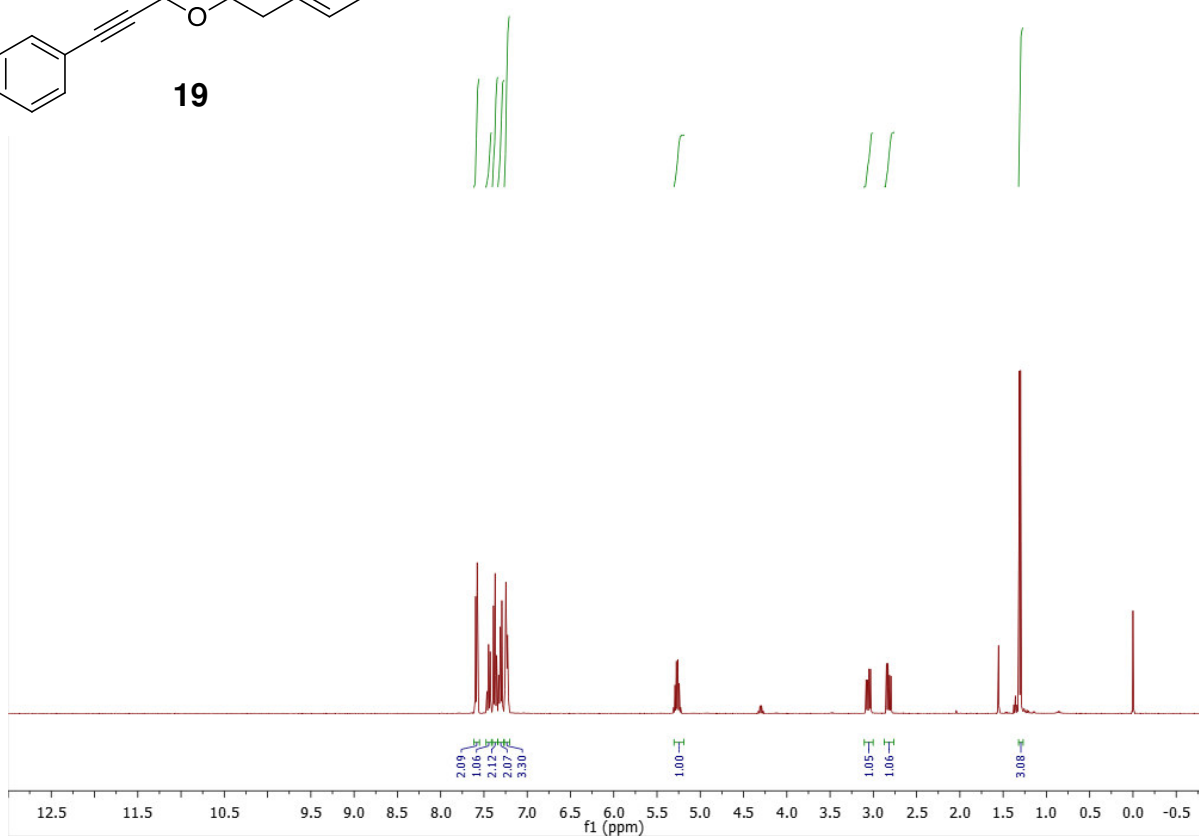
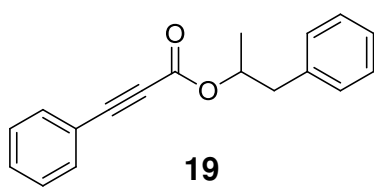




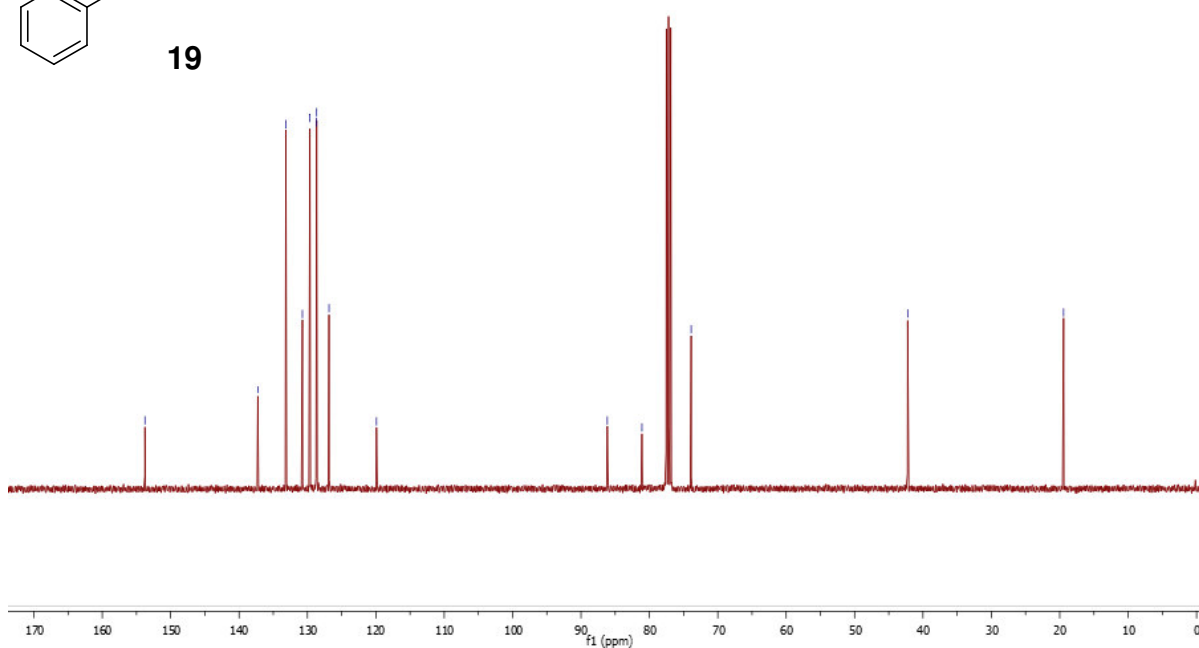
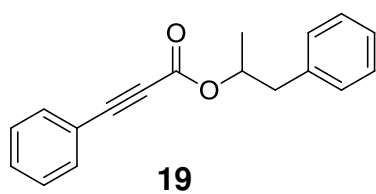


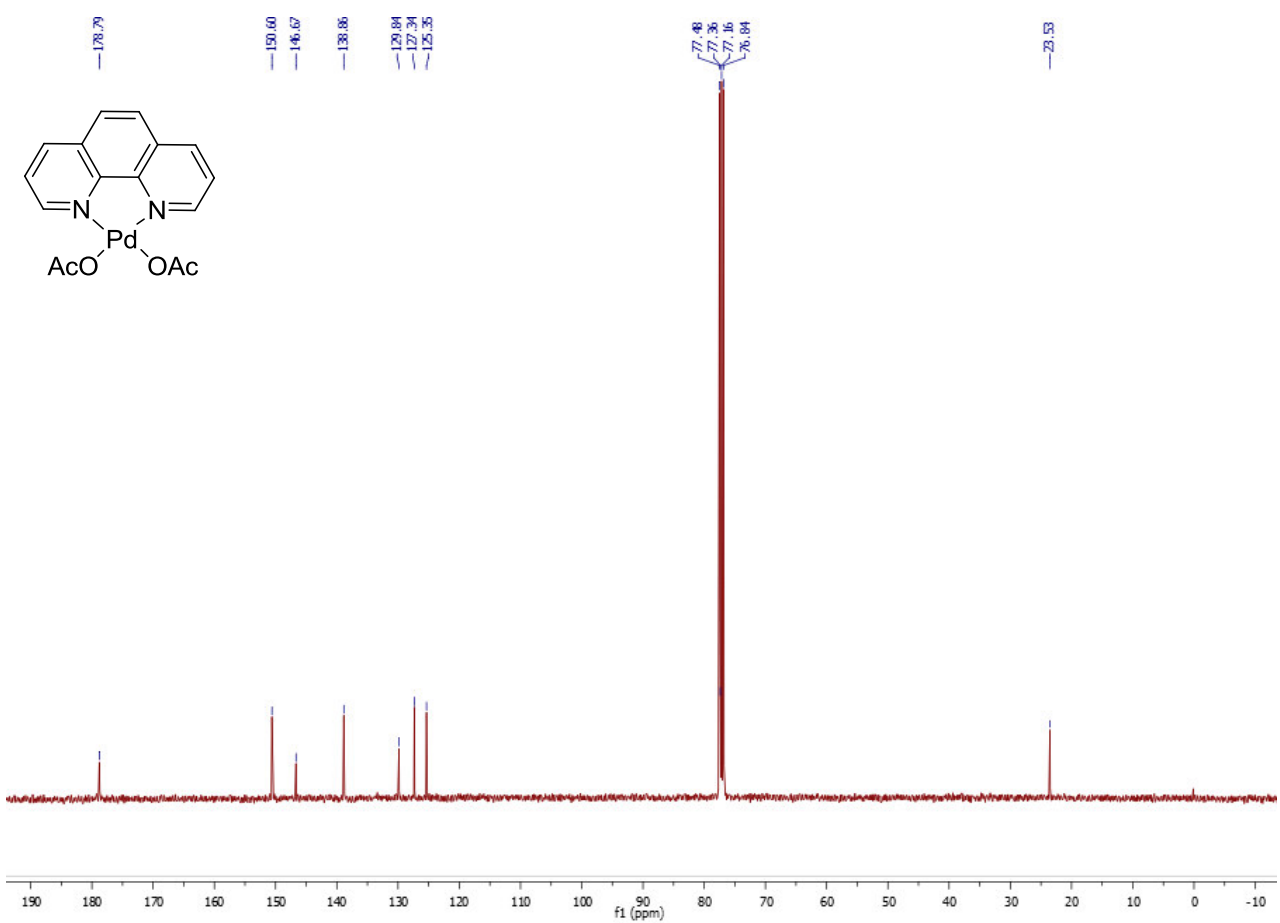
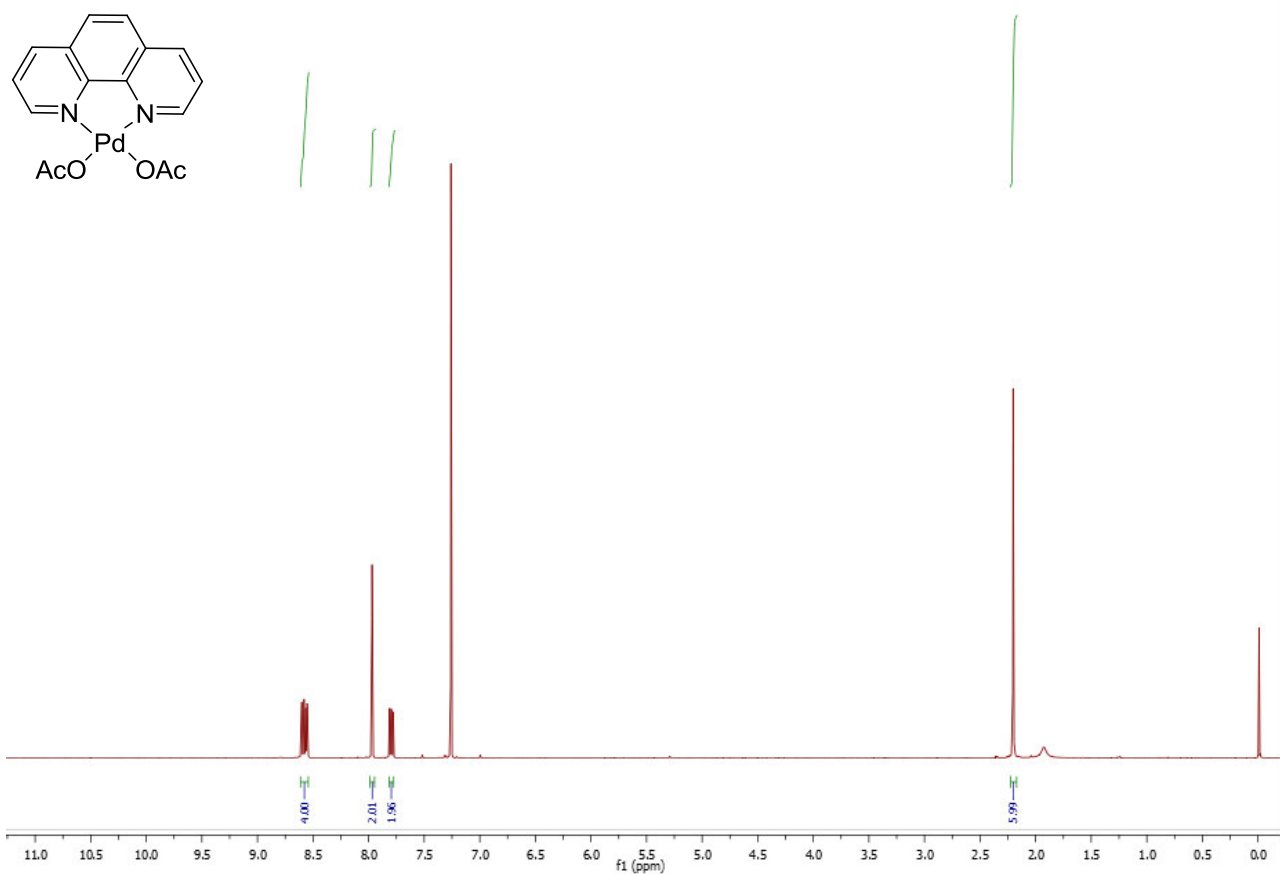




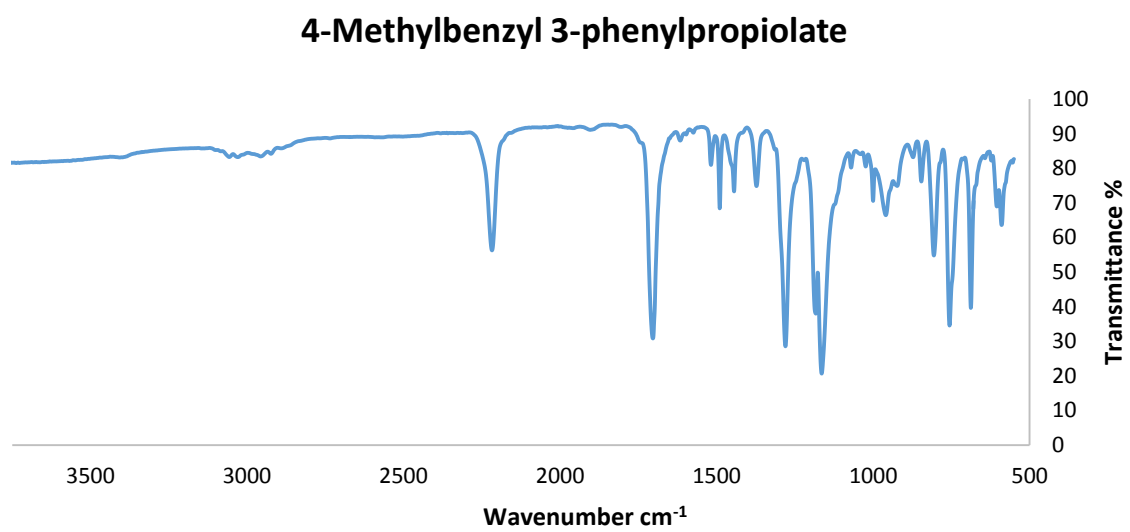


Chemical shift values (ppm) for ¹H NMR: 153.77, 137.25, 133.16, 128.64, 128.72, 128.66, 128.85, 119.91, 86.16, 81.10, 73.90, 42.24, 19.44.





3.5.8 Example IR Spectra



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Chapter 4

Palladium(II) Catalysed Aminocarbonylation of Terminal Alkynes for the Synthesis of 2- Ynamides

4.1 Introduction

4.1.1 Importance of 2-Ynamide Synthesis

2-Ynamides are valuable building blocks that have found application in both organic synthesis and pharmaceutical discovery chemistry. Their potential in natural product synthesis is demonstrated through their use in the preparation of heterocycles. Several examples have been demonstrated within the literature, for example the one step cyclisation of 2-ynamides *via* an intramolecular Heck reductive cyclisation to form 1- substituted 3-benzazepines.¹ (Figure 4.1) This transformation is beneficial, as the 3-benzazepine framework is found in alkaloids² and NMDA (*N*-methyl-D-aspartate) receptor antagonists;³ which have been studied for neurodegenerative diseases.⁴

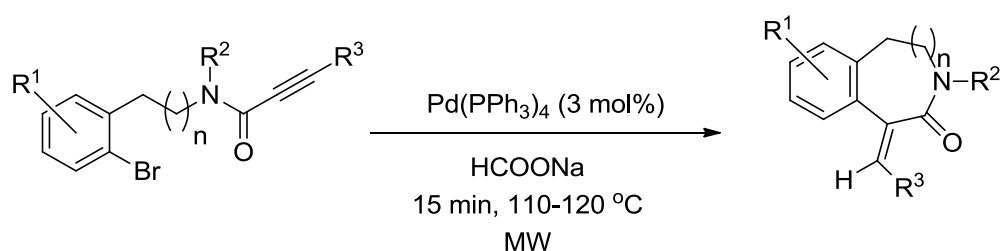


Figure 4.1 Use of 2-ynamides for synthesis of 3-benzazepine framework.

Other examples include the synthesis of α -alkylidene- γ -butyrolactams,⁵ the preparation of 3-(diarylmethylenyl)oxindole⁶ and the tandem fluorination and cyclisation of enynes.⁷ (Figure 4.2) In addition, bicyclic enediynes bearing the 2-ynamide functionality have been suggested to undergo Bergman cyclisation⁸

to form larger heterocyclic molecules, as the presence of the electron withdrawing group enhances the reactivity.⁹

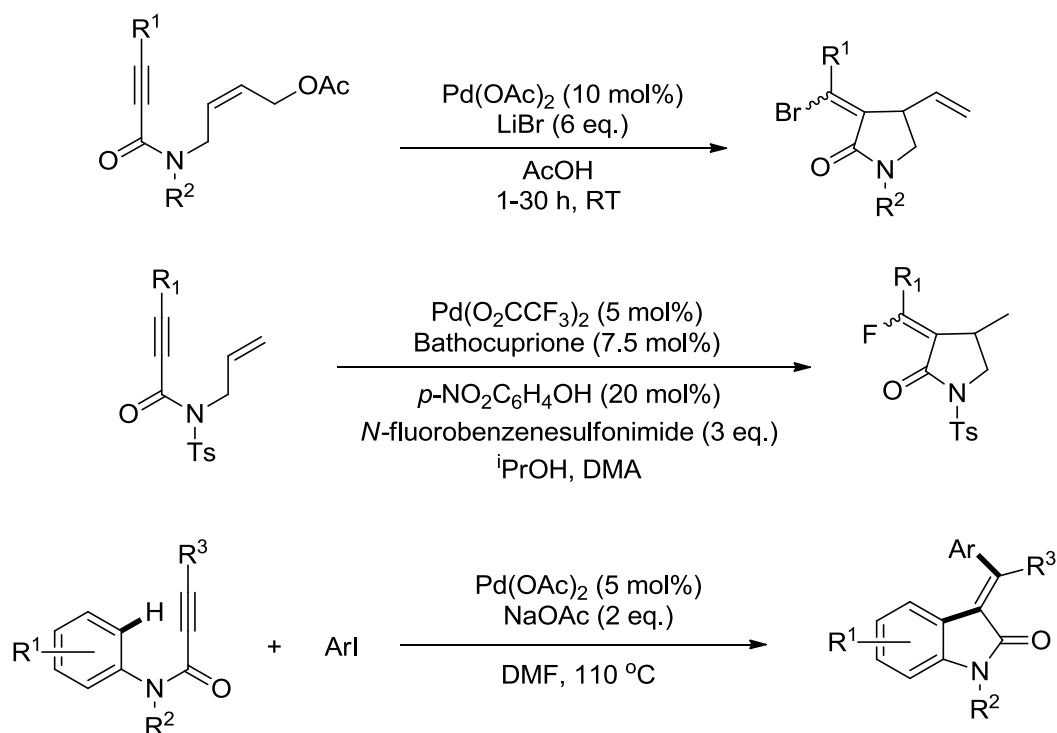


Figure 4.2 Examples of heterocyclic synthesis utilising 2-ynamides.^{5,6,7}

2-Ynamides are also useful intermediates in the synthesis of biologically active molecules. These include examples such as quinolone $\alpha 7$ nicotinic acetylcholine receptor agonists¹⁰ and the immunosuppressant, rapamycin.¹¹ In addition, drug analogues containing the 2-ynamide moiety have been tested for their potential use as protease activated receptor (PAR) antagonists¹² and phosphodiesterase (PDE-5) inhibitors.¹³ (Figure 4.3) Furthermore, 2-ynamides have been utilised in the synthesis of 3,3-diacrylamides, present in fungicides.¹⁴

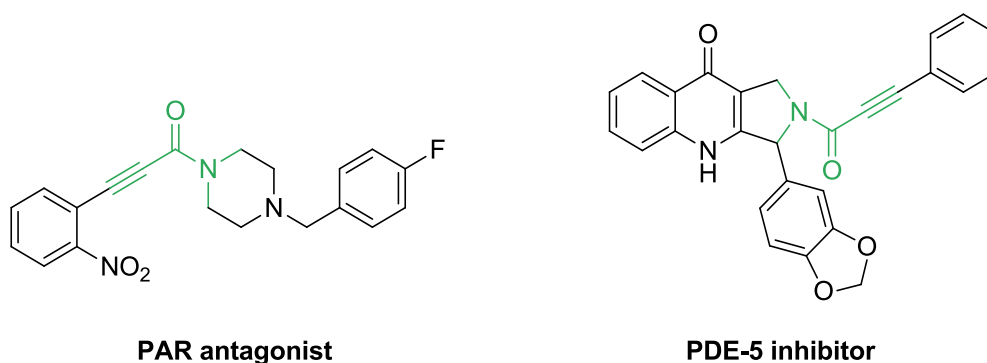


Figure 4.3 Examples of biologically active molecules containing the 2-ynamide functionality.^{12,13}

4.1.2 Non-Catalytic Approaches for the Synthesis of 2-Ynamides

2-Ynamides can be synthesised by the coupling of amines with alkynyl carboxylic acids using *N*-hydroxysuccinimide and *N,N'*-dicyclohexylcarbodiimide (DCC) in 1,4-dioxane at room temperature.¹ The major drawback of this method is the need to firstly synthesise the alkynyl carboxylic acid, as only a limited scope are commercially available. This generally requires the use of alkynyl metal species which can be reacted with CO₂,¹⁵ although more recent methods have been developed that utilise a copper or silver catalyst with a metal carbonate base, and carbon dioxide.¹⁶

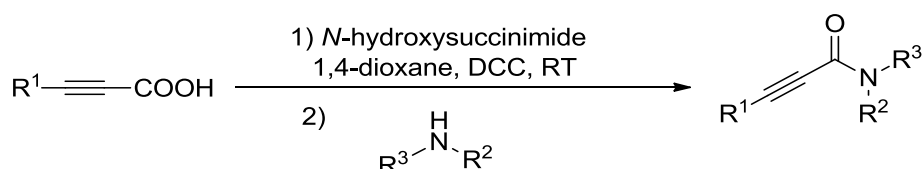


Figure 4.4 Synthesis of 2-ynamides *via* coupling of amines with alkynyl carboxylic acids.¹

Hoberg and Riegel also demonstrated a system that utilised terminal alkynes and amines with stoichiometric amounts of nickel(II) complexes in combination with carbon monoxide.¹⁷ This method, demonstrated the use of CO as an inexpensive way to introduce a carbonyl group into the molecule, however the use of stoichiometric reagents is highly undesirable.

4.1.3 Catalytic Approaches for the Synthesis of 2-Ynamides

Ideally, 2-ynamides should be synthesised by catalytic methods, several examples of which have been reported within the literature. The most commonly utilised method, is a Pd/Cu catalyst system for the reaction of carbamoyl chlorides with terminal alkynes.¹⁸ This method despite being catalytic still has several drawbacks; firstly it requires the use of carbamoyl chlorides which are known to be moisture sensitive, and so require the use of dry solvents and inert reaction conditions. In addition, carbamoyl chlorides are not widely commercially available, and so the scope in terms of amine functionality is limited to simple amines such as dimethyl or diisopropyl.

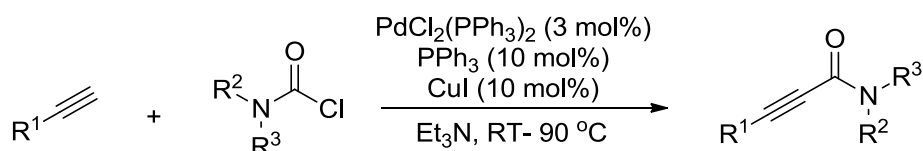


Figure 4.5 Catalytic synthesis of 2-ynamides utilising terminal alkynes and carbamoyl chlorides.^{18b}

More recently, several other catalytic alternatives have been suggested within the literature. The first of these is that of Hwang and co-workers, who demonstrated a catalytic system comprised of $\text{Pd}(\text{OAc})_2$ and silver oxide to form 2-ynamides using alkynyl carboxylic acids, amines and CO.¹⁹ They highlighted the ability to use a wide range of amines, something that was not possible when using carbamoyl chlorides. They did however note that the reaction could not be carried out using primary amines. A variety of alkynyl carboxylic acids were also tested, with electron donating and electron withdrawing groups giving high yields. Lower yields were achieved with the nitrile substituent, and groups containing heteroatoms such as sulfur. (Figure 4.6)

Tentative mechanistic studies were also carried out whereby it was highlighted that in the absence of CO, no product was observed, giving evidence to suggest that the reaction proceeds *via* a carbonylation reaction rather than a

condensation reaction between the amine and acid. The reaction was also carried out using a stoichiometric quantity of $\text{Pd}(\text{OAc})_2$ in the absence of Ag_2O . In this case, only a small amount of product was observed, suggesting that the silver oxide is not only acting as an oxidant, but also potentially as a base.

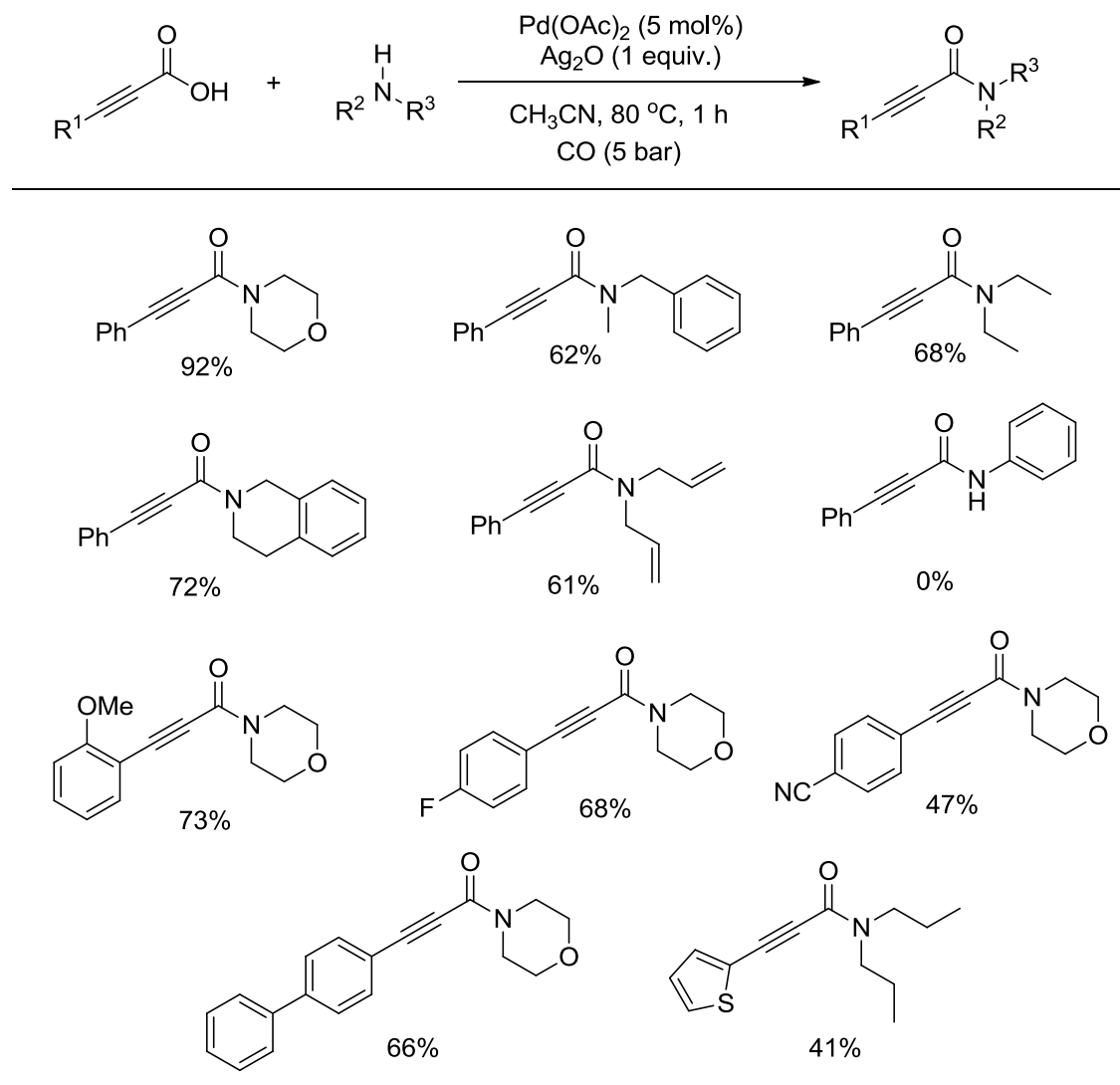


Figure 4.6 Synthesis of 2-ynamides *via* palladium catalysed decarboxylative coupling.¹⁹

An alternative to this system was reported by Ye and co-workers, who demonstrated the use of *tert*-butyl hydrogen peroxide (TBHP) as the terminal oxidant.²⁰ This example utilised terminal alkynes in combination with formamides to produce 2-ynamides *via* cross-dehydrogenative coupling (CDC). The catalyst system was composed of copper chloride, 2,6-

bis(benzimidazol-2'-yl)pyridine (H_2BIP), TBHP, and LiO^tBu (lithium *tert*-butoxide). The screening process highlighted the importance of the presence of a tridentate chelating ligand, and suggested that the imidazole functionality may also play a key role within the reaction. An extensive substrate scope was performed, some examples of which are shown in Figure 4.7. This demonstrated the ability to use both aromatic and aliphatic alkynes to achieve decent yields. Substituted aromatic alkynes containing both electron donating and electron withdrawing groups worked well under the optimised reaction conditions; however it was necessary to increase the reaction time to two hours with aromatic substrates bearing electron withdrawing substituents. In the case of aliphatic substrates, prolonged reaction times and increased LiO^tBu were required to achieve reasonable yields. Functionalities such as esters and nitriles, which can be sometimes sensitive to metal catalysis, could also be tolerated. Pyridinyl alkynes and diethynyl benzenes could not be used.

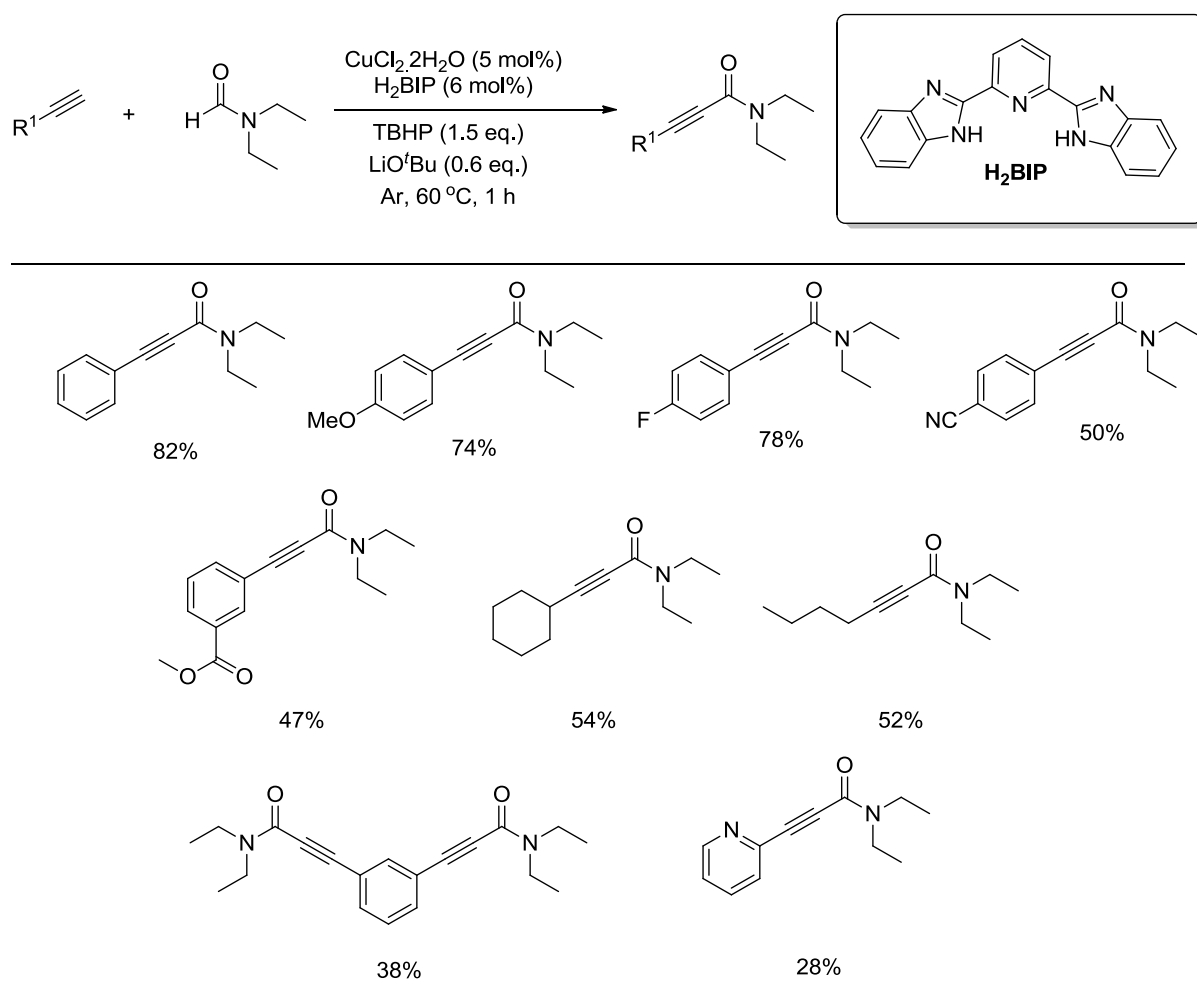


Figure 4.7 Cross-dehydrogenative coupling of terminal alkynes with formamides to synthesise 2-ynamides.²⁰

When *N,N*-diethylformamide (DEF) was substituted for *N*-dimethylformamide (DMF), a dramatic drop in yield of approximately 40% was observed with several alkyne substrates including –OMe, –Br and –Me. Further investigation revealed that a competing reaction was occurring, entailing alkynylation of the C–H bond adjacent to the nitrogen atom, and therefore resulting in a lower yield of the desired product. Reactions were slow when using *N,N*-di-*n*-propylformamide and *N,N*-di-*n*-butylformamide, and were not possible with bulky amides such as *N,N*-diisopropylformamide. This is a major drawback of the suggested catalytic method; not only is the formamide required in a large excess (1:34), but there are also serious limitations with regards to substrate scope.

In both the aforementioned catalytic systems, Ag_2O ¹⁹ and TBHP²⁰ were used as the terminal oxidant. These methods, despite being an improvement on the previously discussed non-catalytic systems, still require an additional oxidant component within the reaction system, thus causing additional cost and waste. An alternative to this was proposed by Dong and co-workers, who reported a system that did not require the use of an external oxidant by utilising Pd(0) as the active species.²¹ They optimised a catalyst system comprised of $\text{Pd}_2(\text{dba})_3$ (tris(dibenzylideneacetone)dipalladium (0)), Xphos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl), Cs_2CO_3 (caesium carbonate), and acetonitrile to allow oxidative carbonylation of bromoalkynes with secondary amines. (Figure 4.8)

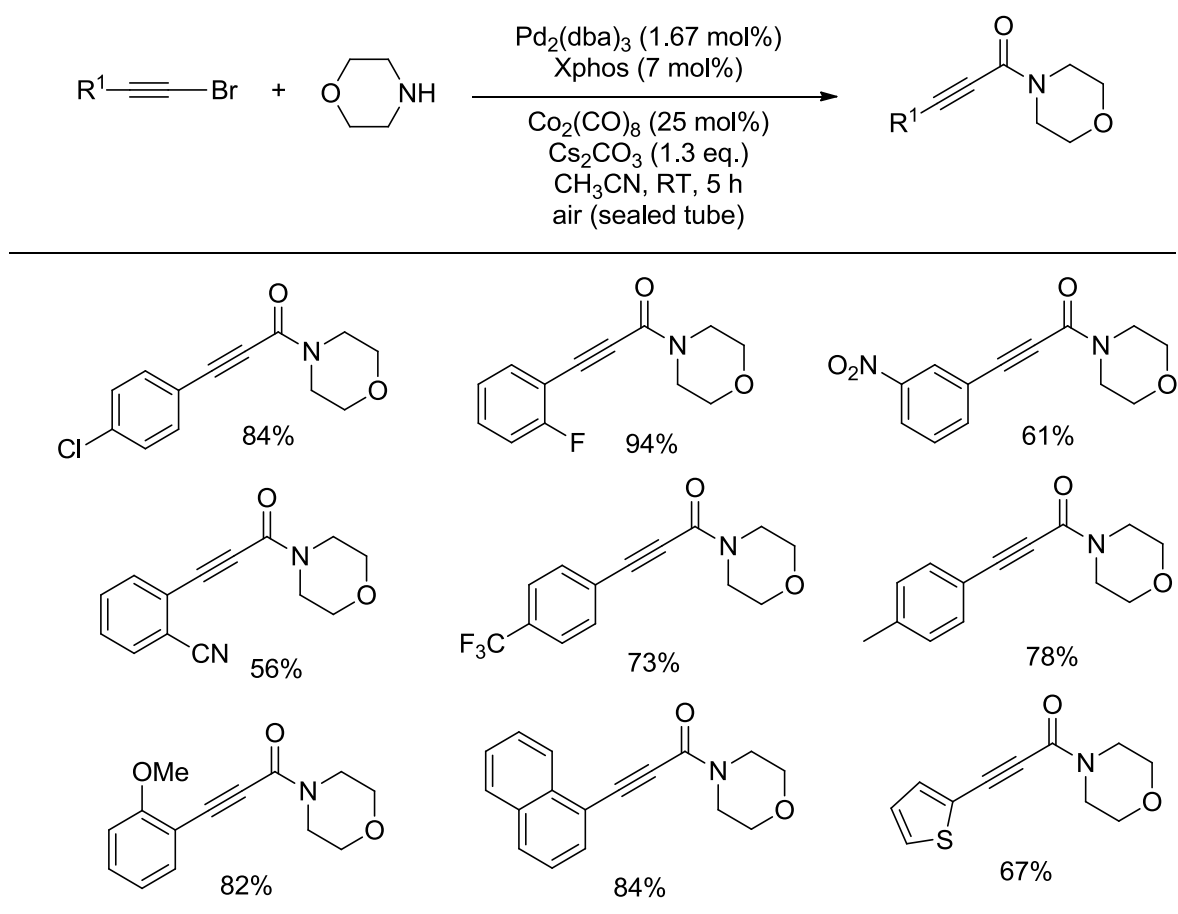


Figure 4.8 Aminocarbonylation of bromoalkynes with amines using $\text{Co}_2(\text{CO})_8$.²¹

Under these conditions, similar yields were achieved to the previously mentioned CDC coupling catalytic method.²⁰ However, in contrast, this method

was not applicable to aliphatic alkynes. A variety of amines could also be used, including aryl amines and cyclic alkyl amines. In addition, primary amines such as *N*-butylamine and cyclohexylamine gave the desired products in 58% and 43% yields respectively. This is interesting as it was the first report of utilising primary amines for aminocarbonylation.

The addition of 1 equivalent of Ag₂O was also investigated, demonstrating that under these conditions, arylpropionic acids could also be combined with amines to give the desired 2-ynamide product. This suggests that in this case, the active species is a palladium(II) intermediate, and the Ag₂O is required to oxidise the Pd(0) precursor.

4.1.4 Catalytic Approaches to 2-Ynamide Synthesis Utilising Oxygen or Air as the Terminal Oxidant

An improvement on using oxidants such as Ag₂O and TBHP, would be to apply molecular oxygen or air as the terminal oxidant, as it is cheap, abundant, non-toxic and the sole byproduct is water. Examples of oxidative carbonylation have been reported whereby oxygen or air is used as the terminal oxidant, and CO gas as the carbonyl source. This is atom efficient in terms of CO also, as carbon monoxide gas is the cheapest, most atom economic way of introducing a carbon atom into a molecule.

It has previously been highlighted that despite oxidative carbonylation methods being used to convert bulk chemicals into fine chemicals on an industrial scale, they are still greatly lacking in organic synthesis.²² Palladium catalysed oxidative carbonylations have the potential to be very useful methods in both an academic and an industrial arena, as they can allow the introduction of several new bonds into a molecule *via* one transformation.²³ Despite this, they have been much less studied than other palladium(II) catalysed oxidation reactions, such as alcohol oxidation.²⁴

There have been a handful of examples within the literature over the last 15 years, demonstrating the use of terminal alkynes with amines and CO gas to directly produce 2-ynamides. This synthetic strategy has several advantages. Firstly, carbon monoxide is readily available, and unquestionably the cheapest

source of the carbonyl functional group. In addition, a diverse range of alkynes and amines are commercially available, this is in direct contrast with the previously mentioned methods that utilise alkynyl carboxylic acids.^{1,19} The first example of catalytic aminocarbonylation was proposed by Gabriele and co-workers in 2001.²⁵ They demonstrated a system comprised of PdI_2 and KI, under a pressure of CO (16 atm) / O_2 (4 atm), at 100 °C in 1,4-dioxane. They showed that under the reaction conditions aryl acetylenes could be used to produce high yields, however the use of alkylacetylenes resulted in a greatly reduced yield; even with a prolonged reaction time. In the case of alkylacetylenes, a competing reaction occurs resulting in the formation of bis-diethylamides of alkyl maleic acid. This means that despite a significant alkyne conversion, the yield of desired product was greatly reduced. (Figure 4.9)

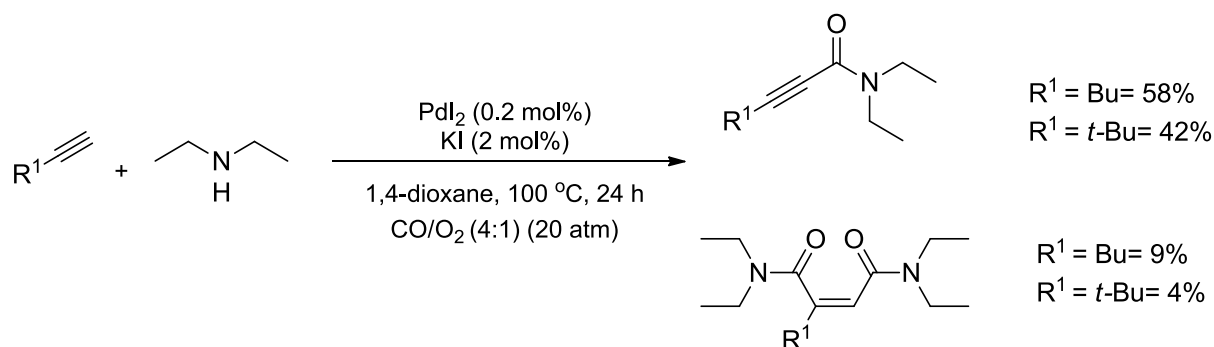
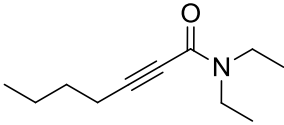
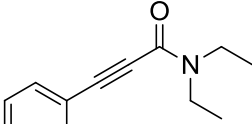
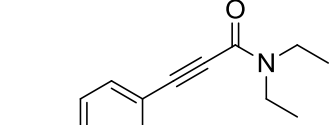
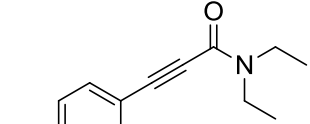
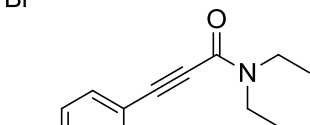
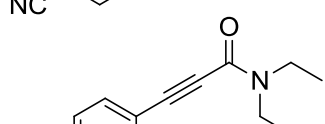
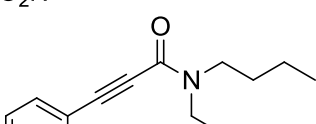
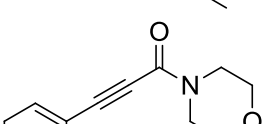


Figure 4.9 Dicarbonylation product formed when using alkylacetylenes.²⁵

It was also noted that there was not a large variance in reactivity when substituting the arylacetylene at the four position with electron donating or electron withdrawing groups. (Figure 4.10) In the case of amines, it was found that strongly nucleophilic secondary amines such as diethylamine were required for a successful reaction. Sterically hindered amines such as diisopropylamine could not be used. As expected, primary amines led to a complex mixture of products.²⁵

$ \begin{array}{c} \text{R}^1\text{—}\text{C}\equiv\text{C—H} + \text{R}^2\text{—}\text{N}(\text{R}^2)\text{—H} \\ \xrightarrow[\text{CO/O}_2 \text{ (4:1) (20 atm)}]{\text{PdI}_2 \text{ (0.2 mol\%)} \\ \text{KI (2 mol\%)}} \\ \text{1,4-dioxane, 100 }^\circ\text{C, 24 h} \end{array} $			$ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{—}\text{C}\equiv\text{C—C—N}(\text{R}^2)_2 \end{array} $	
Product	Alkyne Conversion (%)	Yield (%) ^a		
	71	58(54)		
	90	81(73)		
	83	80(73)		
	82	74(68)		
	95	70(66)		
	100	32(28)		
	90	70(62)		
	93	70(64)		

(a) Numbers in parentheses are isolated yields based on alkyne.

Figure 4.10 Aminocarbonylation of terminal alkynes and secondary amines.²⁵

A mechanism for the reaction was also proposed; substitution of the terminal proton on the alkyne by PdI_2 , followed by insertion of CO leads to an alkynyl palladium species, which is believed to be the reaction intermediate. The amine is then inserted into the palladium carbon bond, and undergoes reductive elimination to give the desired product. The $\text{Pd}(0)$ is then reoxidised by iodine in combination with molecular oxygen. No evidence was given for this proposal, except for the reasoning that the reaction does not occur unless the amine is sufficiently nucleophilic, therefore supporting the first step in the reaction mechanism.²⁵

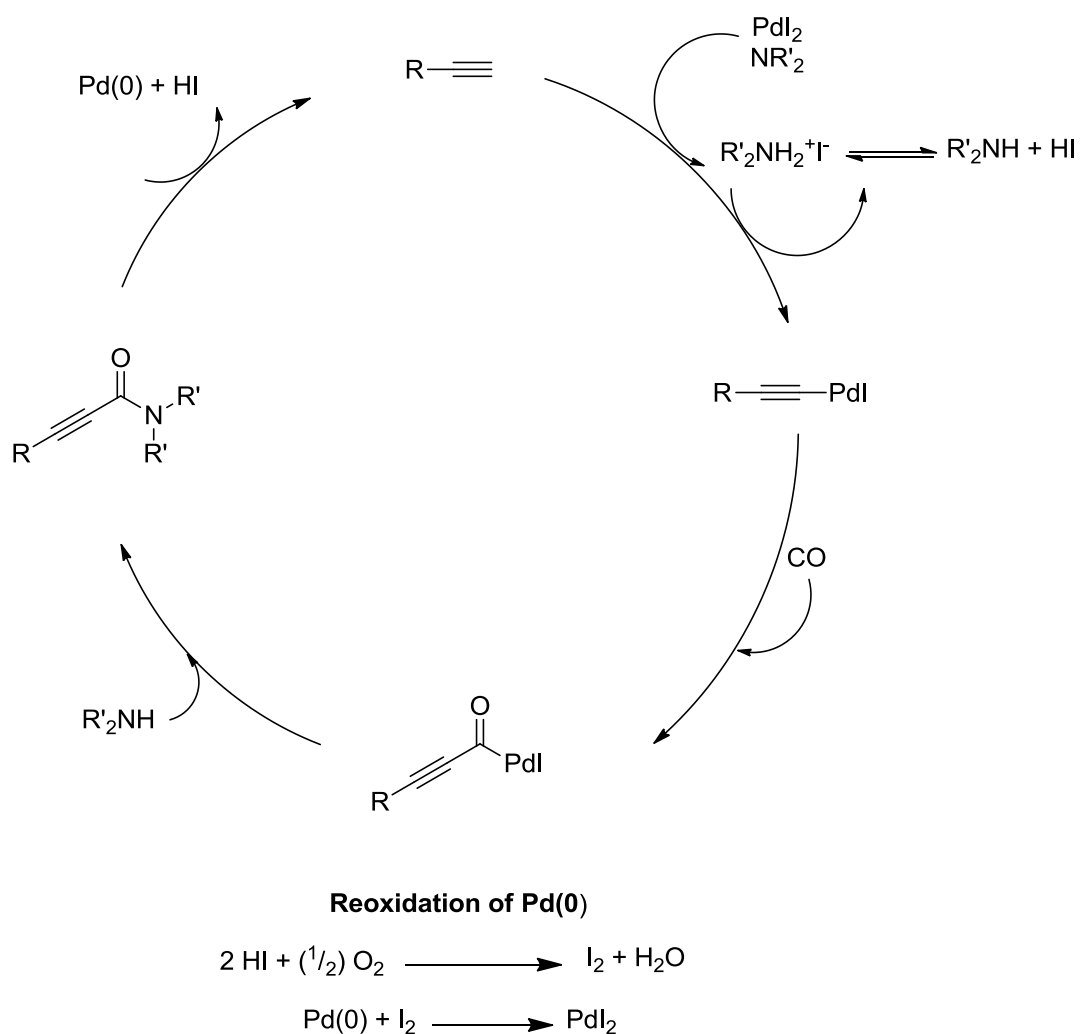


Figure 4.11 Proposed mechanism of aminocarbonylation by Gabriele and co-workers.²⁵

Yamamoto and co-workers showed one example of aminocarbonylation, in a study mainly focussed on the oxidative carbonylation of terminal alkynes with alcohols to give 2-alkynoates.²⁶ (See Chapter 3 for more details) (Figure 4.12)

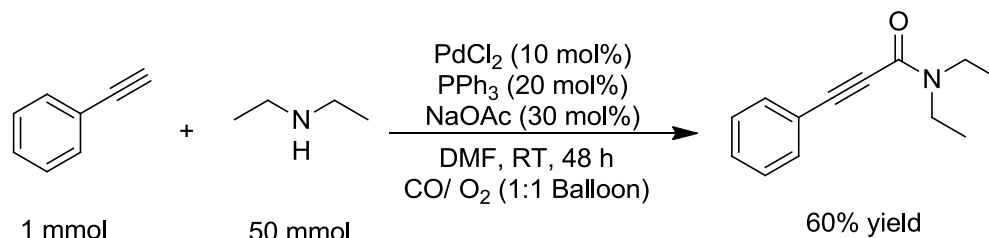


Figure 4.12 Example of aminocarbonylation by Yamamoto and co-workers.²⁶

Although there was only one example of aminocarbonylation reported by Yamamoto and co-workers, it is still an important example, as it was the first reported use of ligands for aminocarbonylation. However, ideally phosphine ligands should not be used under oxidative conditions as they themselves can become oxidised. In this case, the nucleophile was also required in a large excess.

In 2015, Xia and co-workers demonstrated the use of an *N*-heterocyclic carbene (NHC) ligand for aminocarbonylation.²⁷ (Figure 4.13) They suggested that the strong σ -donating ability of the NHC helps to stabilise the Pd(0) and promote oxidation to Pd(II).

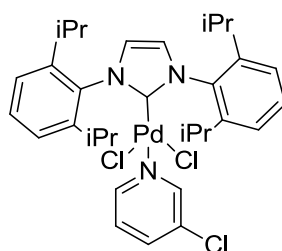
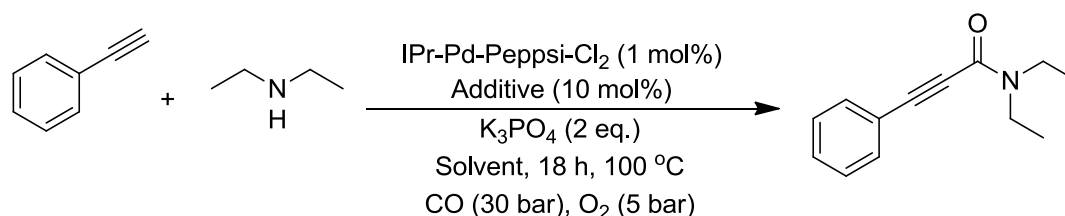


Figure 4.13 *i*-Pr-Pd-Peepsi-Cl₂ ligand.²⁷

The reaction conditions reported were similar to that of Gabriele and co-workers with the exception of the Pd-ligand complex;²⁵ KI, at 100 °C in 1,4-dioxane, under CO (30 bar) :O₂ (5 bar). They also utilised potassium phosphate as an inorganic base additive. During the reaction optimisation

process, several solvents and iodide additives were screened, some highlights of which can be seen in Figure 4.14. In combination with potassium iodide, 1,4-dioxane was shown to be the best solvent. More ‘organic’ iodide salts such as tetrabutylammonium iodide $[\text{NBu}_4][\text{I}]$ gave poor results when using 1,4-dioxane as a solvent.



Additive	Solvent	Yield (%)
KI	1,4-dioxane	95
NaI	1,4-dioxane	60
CuI	1,4-dioxane	10
$[\text{NBu}_4][\text{I}]$	1,4-dioxane	37
KI	DMSO	15
KI	toluene	36
KI	anisole	52
KI	ethyl acetate	30
KI	acetonitrile	<5
KI	tetrahydrofuran	17
KI	ethanol	5

Figure 4.14 Screening results from NHC aminocarbonylation.²⁷

Control reactions showed the iodide anion to be a vital component within the reaction system. The optimised reaction conditions were then used to perform

a substrate scope, testing various alkynes and secondary amines. It was demonstrated that under these conditions, arylalkynes and alkylalkynes could achieve fair to good yields. (Figure 4.15) Both electron donating and electron withdrawing substituents worked well, and the system was shown to be tolerant of –CN group, which has been shown previously to undergo other transformations, such as cyclisation, under similar reaction conditions.²⁸

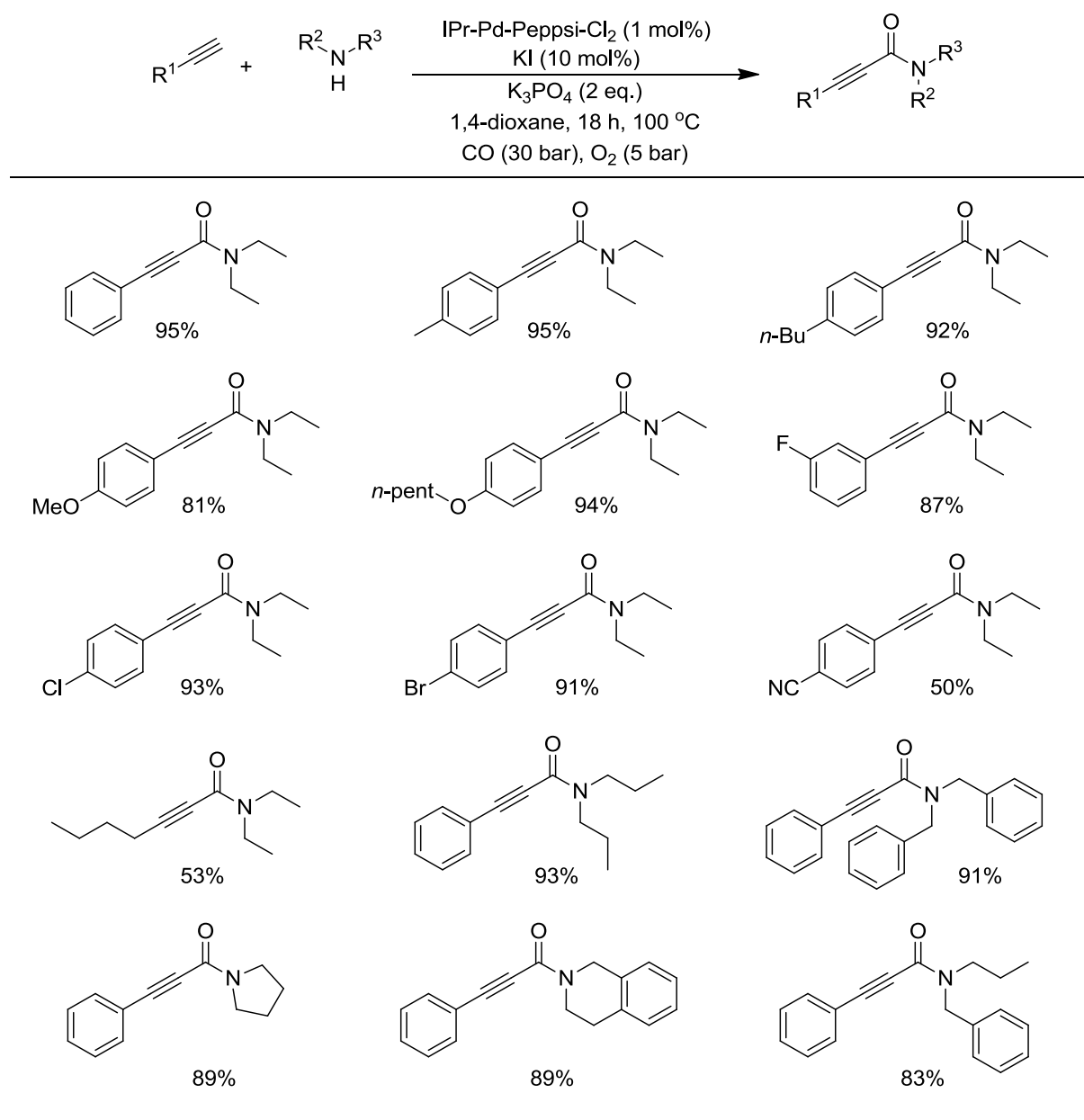


Figure 4.15 Substrate scope utilising IPr-Pd-Peppsi-Cl₂.²⁷

In terms of secondary amines, both symmetrical and unsymmetrical alkyl and aryl amines could be used to achieve high yields. Higher yields are achieved overall than the previously mentioned Gabriele paper.²⁵ Whereas very similar reaction conditions are used, a five times higher loading of the expensive Pd-pepsi complex and KI additive are employed here. It is however interesting to note that both papers use a 1:10 ratio of Pd:KI, and both operate at 100 °C in 1,4-dioxane, under a CO rich atmosphere.

The authors also proposed a reaction mechanism based on ESI-MS (electrospray mass spectrometry) studies. They observed two peaks which could be due to the two palladium species shown in Figure 4.16.²⁷

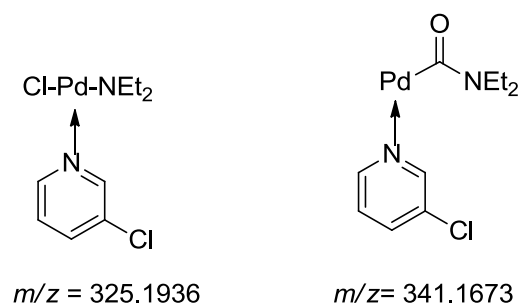


Figure 4.16 Species observed during ESI-MS studies.²⁷

Xia and co-workers suggest that these observations support that the amine has the potential to attack the co-ordinated carbonyl group in the NHC-Pd centre. This is thought to be attributed to the strong σ -donating properties of the NHC ligand. The suggested mechanism is shown in Figure 4.17.

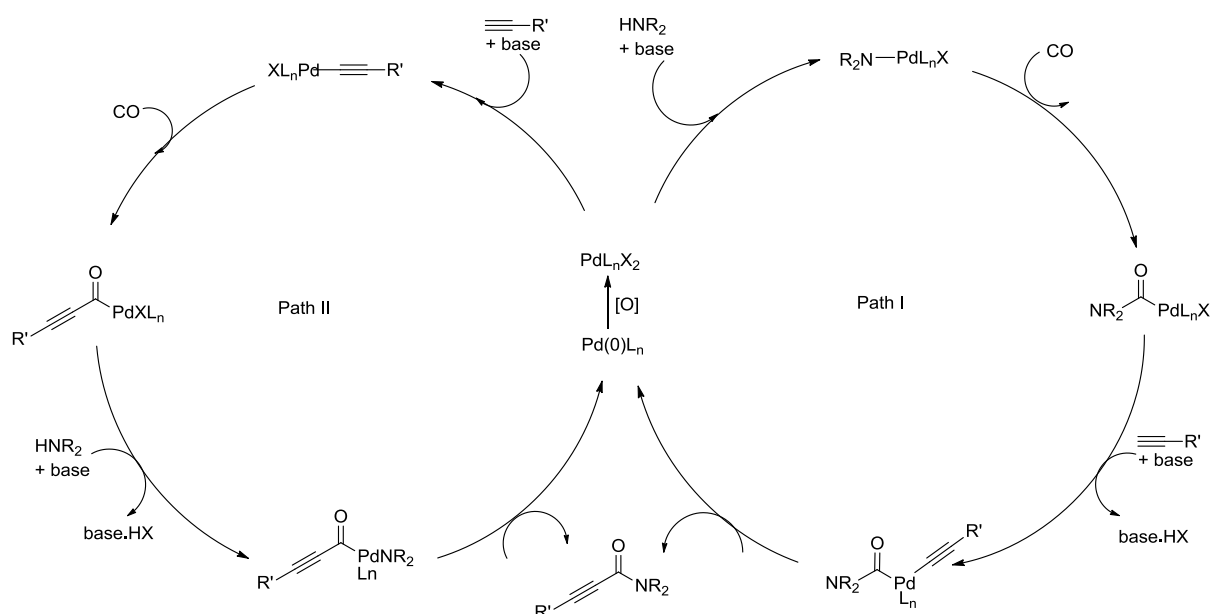


Figure 4.17 Proposed reaction mechanism based on ESI-MS studies.²⁷

This reaction mechanism differs to that suggested by Gabriele²⁵ and co-workers whereby in this case the N-H bond is firstly broken to allow formation of the amine-Pd species. This undergoes CO insertion, followed by displacement by the alkyne to give the alkynyl palladium intermediate species. This then undergoes reductive elimination to give the desired product, and Pd(0).²⁷ The Pd(0) is then thought to be reoxidised by iodine and oxygen, as also suggested by Gabriele and co-workers.²⁵

In 2012, Gadge and Bhanage introduced a heterogeneous system that utilised Pd/C and $[\text{NBu}_4][\text{I}]$.²⁹ They highlighted that this system allowed for facile separation of the palladium catalyst before reuse, and did not require the use of expensive or air sensitive phosphine ligands. As with the previously mentioned aminocarbonylation reaction systems^{25,27} they also operated under a CO rich atmosphere of CO (5 atm): O₂ (1 atm).

They performed an extensive reaction optimisation, exploring reaction temperature, iodide additive, solvent, reaction time, and catalyst loading. They found a lower reaction temperature of 80 °C to be preferable. However it required a prolonged reaction time of 14 h, and the need to use 1,4-dioxane as a solvent. Interestingly, they found $[\text{NBu}_4][\text{I}]$ to give the best results in 1,4-

dioxane, even over KI. This is interesting as it is in direct contrast to that found by Xia and co-workers.²⁷ When air (1 atm) was applied as an alternate oxidant to O₂, the yield was greatly reduced with the more dilute oxygen mixture. The final optimised reaction conditions can be seen in Figure 4.18.

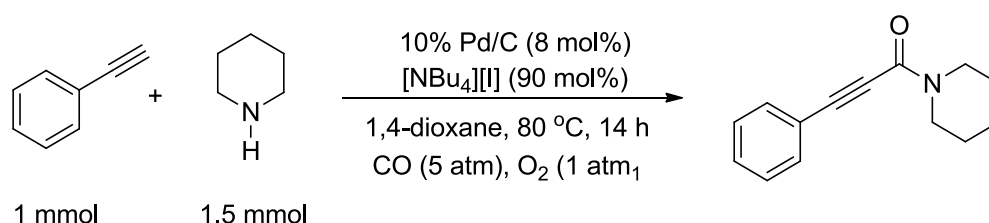


Figure 4.18 Optimised conditions for heterogeneous Pd/C system.²⁹

The reaction system proved applicable to aromatic and both linear and cyclic aliphatic amines. Unsymmetrical amines could also be used; in the case of *N*-methyl-1-phenylmethanamine and 1,2,3,4-tetrahydroisoquinoline, the corresponding amides were produced as a 1/1 mixture of E/Z rotamers around the amide bond.²⁹ As was found previously by Gabriele and co-workers,²⁵ sterically hindered amines and less nucleophilic amines did not provide any reaction.²⁹ A small selection of alkynes were also tested. As expected, 1-hexyne was less reactive than the aromatic alkynes tested. This is in agreement with that found by both Gabriele²⁵ and Xia.²⁷ 4-Ethynyl-*N,N*-dimethylaniline and 3-ethynylanisole gave high yields of 94% and 88% respectively. The system was also shown to be tolerant of N atoms, demonstrated through the use of 5-ethynylimidazole (94%). Overall, this system achieved similar yields to those already mentioned, however its major benefit was the ability to recycle the Pd/C catalyst. The catalyst was used up to four times with only 6% decline in reactivity between the 1st and 4th run. After the 4th run, the filtered solution was examined for evidence of catalyst leaching through the use of ICP (inductively coupled plasma atomic emission spectroscopy). This example demonstrates the potential for catalyst recycling with aminocarbonylation systems.

Recently, the same group reported the use of Pd/C in combination with KI in acetonitrile. This system was applied to tertiary amines, (i.e. the reaction

required an *N*-dealkylation step) which resulted in the formation of a mixture of products when employing unsymmetrical amines.³⁰

Overall, the examples discussed show the possible application of aminocarbonylation for the preparation of 2-ynamides, however they still have some problems to be overcome before they can become a more commonly practiced synthetic strategy.

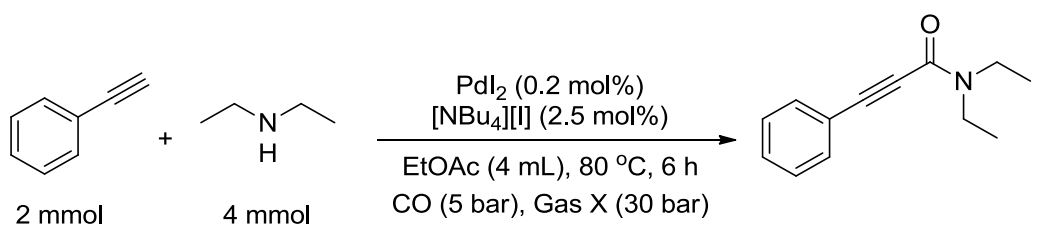
4.2 Aims and Objectives

The aims of this project were to improve some of the features of the work to date, which may ultimately limit its wider application. The first of these was the reaction solvent. Many of the examples in the current literature use DMF, or ethereal solvents such as 1,4-dioxane. This is a major problem, as ethereal solvents under oxidative conditions come with serious safety concerns. An additional problem in terms of reaction safety, is the use of high pressures of oxygen or air, in combination with another flammable gas, CO in the presence of organic solvents. In the procedures already discussed, pure oxygen or air is used in ratios considered to be outside of the suggested safety guidelines. These issues may seem manageable on a small lab scale, however the objective of the study was to optimise a reaction system that could perhaps lead the way for this type of catalyst system to be considered on an industrial scale. We hoped to do this by applying a greener safer solvent, and to utilise oxygen as the terminal oxidant in a safer manner than that reported previously.

4.3 Results and Discussion

The reaction optimisation was commenced utilising phenylacetylene and diethylamine as the model reaction in the presence of PdI_2 (0.2 mol%), and $[\text{NBu}_4][\text{I}]$ (2.5 mol%). The reaction was initially run at 80 °C, in ethyl acetate, for six hours with a 1:2 ratio of alkyne to amine. We firstly tested gas composition, comparing air with a diluted oxygen mixture of 8:92 $\text{O}_2:\text{N}_2$. As can be seen in Table 4.1, little difference was observed between the two gas mixtures, this indicates that the reaction is not mass transfer limited in oxygen, suggesting that the rate limiting step of the reaction is not the re-oxidation of the $\text{Pd}(0)$. This was further confirmed by testing the reaction at three different stir rates – 300 rpm, 600 rpm and 1000 rpm. At all stir rates, the same yield was obtained. If the reaction was mass transfer limited in oxygen, the faster rate would be expected to have a higher yield, and the slow rate, a lower yield. This is important to consider, as if the reaction system is limited in oxygen $\text{Pd}(0)$ aggregation will occur, causing deactivation of the catalyst, thus resulting in a lesser performance.³¹ Whereas ideally, initial rates would be used to confirm no presence of mass transfer limitations regarding oxygen, in this case, checking final yield is sufficient as death of the palladium catalyst due to lack of oxygen would result in a lesser yield.³¹

Table 4.1 Influence of gas mixtures on catalytic performance.



Gas Mixture X	Alkyne Conversion [%] ^a	Yield of Product [%] ^a
Air	78	78
8:92 $\text{O}_2:\text{N}_2$	76	75

[a] Conversion and yield were determined by GC using biphenyl as an internal standard. All results shown are an average of two experiments.

It can also be noted that the reaction under these conditions is highly selective. From these results we decided to proceed using a diluted oxygen concentration of 8:92 O₂:N₂. The ability to perform the reaction under dilute oxygen mixtures is a major advantage, as there are many safety concerns regarding the use of organic solvents, under high oxygen pressures. This shall be discussed later in greater detail.

Next we examined the effect of the counterion on the palladium salt, as can be seen in Table 4.2. It was observed that the reaction occurred with all of the palladium salts tested, however the best results were obtained when using carboxylate anions such as acetate. We had previously noted when optimising the oxidative carbonylation system for the preparation of 2-alkynoates, that acetate was a necessary component within the reaction mixture.³² This has been noted previously in other oxidative carbonylation systems; acetate is a key component, either as the Pd salt counterion, or as an additive, most commonly sodium acetate.^{26,33}

Table 4.2 Effect of Pd counterion on catalytic performance.

<div><div><div>Ph—C≡C—</div><div>2 mmol</div></div><div>+</div><div><div><div>CH₃CH₂NHCH₂CH₃</div><div>H</div></div><div>4 mmol</div></div><div><div><div>PdX₂ (0.2 mol%)</div><div>[NBu₄][I] (2.5 mol%)</div><div>EtOAc (4 mL), 80 °C, 6 h</div><div>CO (5 bar), 8% O₂ in N₂ (30 bar)</div></div><div>→</div><div><div><div>Ph—C≡C—C(=O)N(CH₂CH₃)₂</div></div></div></div></div>		
Counterion X ⁻	Conv. alkyne [%] ^a	Yield of product [%] ^a
I ⁻	76	75
Cl ⁻	71	66
<div><div><div>O</div><div> </div><div>F₃C—C—O⁻</div></div></div>	77	73
<div><div><div>O</div><div> </div><div>CH₃—C—O⁻</div></div></div>	87 ^b	86 ^b
	77 ^c	68 ^c
<div><div><div>O</div><div> </div><div>C(CH₃)₃—C—O⁻</div></div></div>	86	84
<div><div><div>O</div><div> </div><div>CH₃CH₂—C—O⁻</div></div></div>	79	73

[a] Conversion and yield were determined by GC using biphenyl as internal standard

[b] Pd(OAc)₂ of purity > 99.9%

[c] Pd(OAc)₂ of purity 99%

All results shown are an average of 2 experiments

In this case, the carboxylate anion is not a necessity for good catalytic performance however in most cases still gave higher yields than the other salts tested. It has been noted previously that acetate can be used as a reactivity switch in hydration and dimerisation reactions of terminal alkynes.³⁴ In these reported cases, the acetate is essentially working as an internal base. It is possible that in this case, it improves the yield by acting as an internal base to cause activation of the terminal alkyne. However, as the carboxylate anion

demonstrates only a small effect when using an amine nucleophile, it could be considered that its importance in the synthesis of 2-alkynoates is in relation to the alcohol. It is possible that the acetate is required for deprotonation of the alcohol, as this is commonly observed in Pd(II) catalysed alcohol oxidation.³⁵ We decided to proceed using Pd(OAc)₂, and as a result of this decided to compare salt purity of >99.9% against 99%. As can be seen in Table 4.2, there is a considerable difference when using the salt of higher purity. This is of interest, as the importance of Pd(OAc)₂ purity has recently been discussed within the literature.³⁶ This is discussed in greater detail, in Chapter 3. Note, this may be another reason as to why the acetate outperforms some of the other salts tested. The other salts shown are not available in higher purities than those applied, it may be that in this case the acetate salt is simply purer, resulting in an increased yield.

We then investigated the effects of ligands, as we had previously found that ligands played a dramatic role in the synthesis of 2-alkynoates, with tetramethylethylenediamine (TMEDA) giving the best result.³² Reported ligands for the synthesis of 2-ynamides include triphenylphosphine²⁶ and the NHC peepsi ligand, discussed previously.²⁷ However, we hoped to move away from the use of phosphine ligands as these can be easily oxidised under oxidative conditions, thus resulting in loss of active ligand. With regards to the NHC ligand, these can be expensive if pre-bought, and add to the overall cost of the reaction system; rendering them unfeasible on a larger scale. We tested ligands that had performed well under the conditions for the synthesis of 2-alkynoates; 1,10 phenanthroline, neocuproine, 1,8- diazobicycloundec-7-ene (DBU) and tetramethylethylenediamine (TMEDA). These can be seen in Figure 4.19 below.

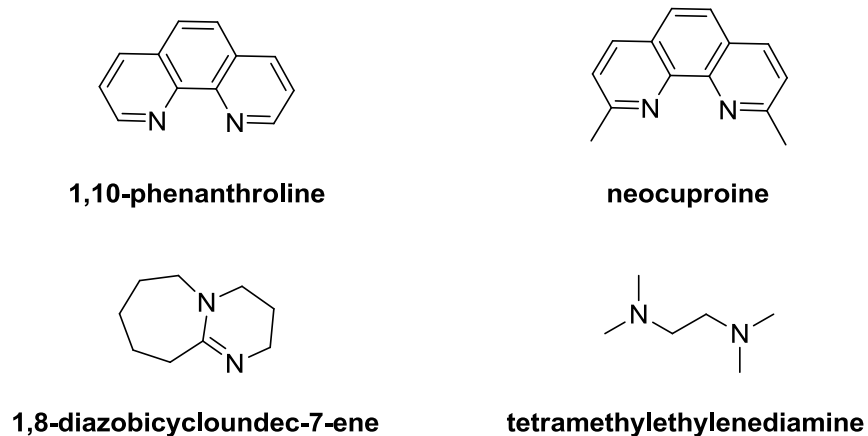
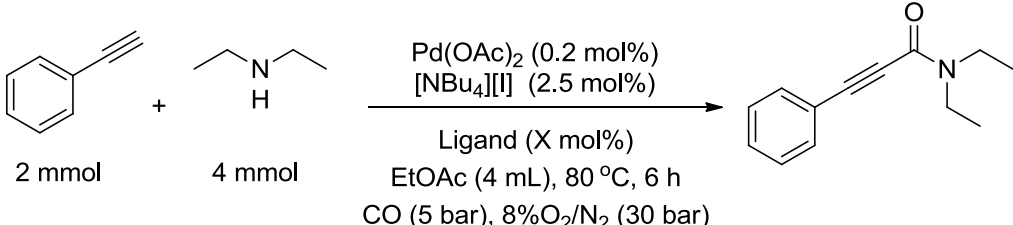


Figure 4.19 Ligands used in ligand screening.

Table 4.3. Ligand Screening.



Ligand	X mol%	Equivalents ^a	Alkyne Conversion [%] ^b	Product Yield [%] ^b
1,10- Phenanthroline	0.2	1	76	72
Neocuproine	0.2	1	81	73
DBU	0.4	2	86	80
TMEDA	2	10	81	79
None	/	/	87	86

[a] Equivalents in relation to Pd(OAc)₂

[b] Conversion and yield were determined by GC using biphenyl as an internal standard

All results shown are an average of two experiments

All the ligands tested gave high yields, however the highest yield achieved (DBU) was still lower than using no ligand; in addition the selectivity with DBU

was lower. It should be noted that the ligands tested, were used in varying equivalents in relation to the palladium loading. For example, 2 equivalents of the monodentate ligand DBU was used, in comparison to 1 equivalent of both bidentate ligands, 1,10 phenanthroline and neocuproine. This was to equalise the amount of available ligating sites. In the case of TMEDA, 10 equivalents were used, as we had found this to previously be very successful with the 2-alkynoate system.³² It is possible that the reason no improvement is observed with the addition of a ligand, is because the amine substrate can act itself as a ligand. Bearing this in mind, we compared using a 1:1 ratio of substrates, to a 1:2 ratio of substrates. The results can be seen in Table 4.4.

Table 4.4 Effect of ratio of substrates on reaction performance.

X [mmol]	Y [mmol]	Alkyne Conversion [%] ^a	Product Yield [%] ^a
2	2	52	47
2	4	87	86

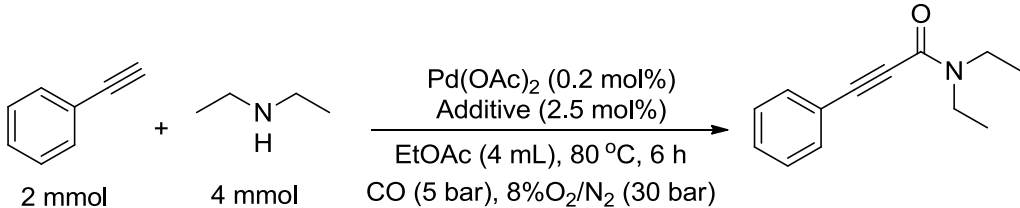
[a] Conversion and yield were determined by GC using biphenyl as an internal standard. All results shown are an average of 2 experiments.

It was observed that the reaction greatly benefited from a 2:1 ratio of amine to alkyne. This suggests again that the amine may also be acting as a ligand, and so is required in excess. From this we chose to proceed using a 2:1 ratio of amine to alkyne, and not use an additional ligand.

We were aware of the benefits of iodide from our work with 2-alkynoates³² and other previous oxidative carbonylation literature.^{29,37} We tested a variety of iodide additives, as can be seen in Table 4.5 below. KI was used as an additive by both Gabriele²⁵ and Xia,²⁷ however it can be observed that when using KI under our conditions, very little of the desired product was obtained. This could

perhaps be attributed to the low solubility of KI in our chosen reaction solvent, ethyl acetate. In our case, the best result was obtained when using $[\text{NBu}_4][\text{I}]$ as the additive; this was previously observed by Gadge and Bhanage when using a heterogeneous Pd/C catalyst system.²⁹

Table 4.5 Effect of additives on catalytic system.

		
Additive	Alkyne Conversion [%] ^a	Yield of Product [%] ^a
None	24	1
$[\text{NBu}_4][\text{I}]$	87	86
$[\text{NBu}_4][\text{Br}]$	39	22
$[\text{NBu}_4][\text{OAc}]$	9	3
KI	34	1
KI/ $[\text{NBu}_4][\text{OAc}]^{\text{b}}$	9	3

[a] Conversion and yield were determined by GC using biphenyl as an internal standard.

[b] 2.5 mol% of both KI and $[\text{NBu}_4][\text{OAc}]$ used.

All results shown are an average of two experiments.

Several examples exist within the literature that demonstrate the use of iodide additives for oxidative carbonylation reactions. The most efficient iodide additive in each case, appears to be dependent on the solvent choice, thus supporting the idea that in our case $[\text{NBu}_4][\text{I}]$ is best due to its solubility. For example, in a biphasic system reported by Chaudhari and co-workers, NaI was found to be the best promoter, when tested against several others such as iodine, CH_3I , $\text{C}_2\text{H}_5\text{I}$ and KI.³⁷ Again in this case, the addition of an iodide promoter was found to be crucial for the progress of the reaction. In a report by Alper and co-workers on mono- and double oxidative couplings of amines

to form ureas and oxamides, they highlighted the reaction to be ‘sluggish’ in the absence of the iodide anion.³⁸ They also showed that by replacing KI with [NBu₄][I], the reaction rate was so greatly enhanced that it could be run at room temperature, and in a variety of solvents.

To the best of our knowledge there is not yet any experimental understanding as to the role of iodide within the oxidative carbonylation reaction system. In a report of alkoxycarbonylation of *N*-vinylphthalimide,³⁹ Jiang and co-workers highlighted the importance of anion co-ordinating ability, demonstrating that the catalytic activity was greatly improved when replacing strongly co-ordinating anions such as F⁻ with weakly co-ordinating I⁻. They reported a large difference in selectivity when moving from [NBu₄][Cl] to [NBu₄][I].³⁹ This was observed in our case when switching from Br⁻ to I⁻.

The most frequently suggested role, is the reoxidation of Pd(0) using iodide ions in combination with molecular oxygen, as can be seen in Figure 4.20.

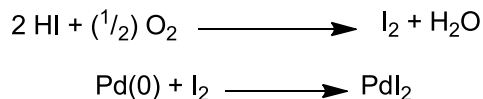
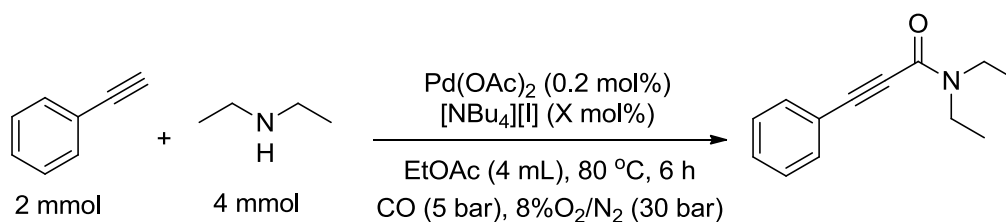


Figure 4.20 Reoxidation of Pd(0) by iodide and molecular oxygen.^{25,37}

This example shows the regeneration of PdI₂. In many literature examples PdI₂ is the palladium salt of choice.²⁵ However, an example of using Pd(OAc)₂ with NaI suggested that intact PdI₂ is formed *in situ*, whereby the acetate anions are displaced by iodide.³⁷ This may be what is occurring under our reaction conditions also, as Pd(OAc)₂ and [NBu₄][I] are used. It is evident that further mechanistic investigations are necessary to fully understand the role of the iodide anion.

We also optimised the ideal quantity of [NBu₄][I], in the previous 2-alkynoate study we found a 1:10 ratio of Pd:[NBu₄][I] to be the optimum.³² The results of this optimisation can be seen in Table 4.6.

Table 4.6 Optimisation of tetrabutylammonium iodide additive loading.

$[\text{NBu}_4][\text{I}]$ [mol%]	Conversion of Alkyne [%] ^a	Yield of Product [%] ^a
0.5	63	56
1	60	56
1.25	81	74
1.5	79	74
2	72	69
2.5	86	85
5	89	85
10	72	63
20	73	73
25	75	72
50	65	65
100	58	59

[a] Conversion and yield were calculated by GC using biphenyl as an internal standard. All results shown are an average of two experiments.

The optimisation showed 2.5 mol% to be best, lower amounts demonstrated a decreased selectivity and 5 mol% was identical to 2.5 mol%, therefore didn't

warrant doubling the additive loading. This is roughly a 1:10 ratio of Pd: [NBu₄][I]. It has been shown previously that the ratio of Pd: iodide promoter can be vital, with the catalyst activity reaching a peak, and then decreasing again if the iodide concentration is too high.^{37,40} The same was observed here with quantities higher than 10 mol%.

In an attempt to further understand the role of iodide within the reaction system, we carried out some additional studies. It has previously been proposed by Gabriele²⁵ and Xia²⁷ that the possible first step in the mechanism is the formation of an alkyne palladium species. (Figure 4.21)

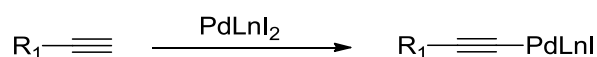


Figure 4.21 Suggested first step of the reaction mechanism.²⁷

We believed that if this were the case, then perhaps, use of [NBu₄][I] additive, would result in an increased rate of alkyne-Pd formation (Figure 4.22), by forming an iodoalkyne species as a reaction intermediate, (step 1) resulting in an increase in the rate of attack by the palladium, (step 2) due to acting as a superior leaving group.

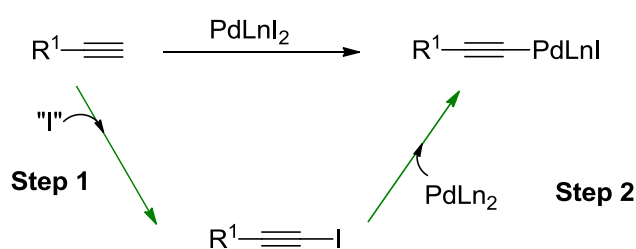
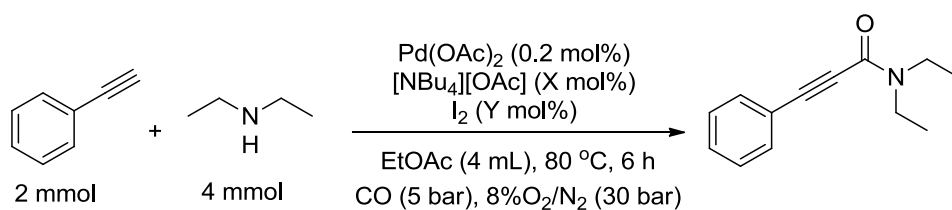


Figure 4.22 Hypothetical mechanism involving iodoalkyne.

We tested this theory by synthesising (iodoethynyl)benzene, and using it in the reaction in place of tetrabutylammonium iodide and phenylacetylene. This reaction showed no activity. A control was also carried out with the addition of [NBu₄][I], however only a 2% yield was achieved. This suggests the reaction does not proceed *via* this mechanistic pathway.

We wondered if the iodine was acting as the oxidant as previously suggested, however controls with stoichiometric quantities of I_2 in the absence of oxygen showed this not to be the case. We did however find that if both iodine and $[NBu_4][OAc]$ were added to the reaction, high yields could be achieved, in the presence of oxygen. We tested various mol% and ratio of $I_2:[NBu_4][OAc]$, the results of which can be seen in Table 4.7.

Table 4.7 Various I₂: $[\text{NBu}_4][\text{OAc}]$.

$[\text{NBu}_4][\text{OAc}]$ [X mol%]	I ₂ [Y mol%]	Conversion of Alkyne [%] ^a	Yield of Product [%] ^a
0.5	0.5	76	76
1	1	78	77
1.5	1.5	63	76
2	2	65	66
2.5	2.5	42	45
10	10	43	43
25	25	28	30
50	50	26	27
100	100	19	19
2.5	5	21	16
5	10	25	20
10	5	81	77
5	2.5	83	75
2	1	87	86

[a] Conversion and yield determined by GC with biphenyl internal standard.

As can be seen, when using the same ratio of iodine to $[\text{NBu}_4][\text{OAc}]$, the optimum loading is 1 mol%. Once increased, the reactivity gradually decreases. The reaction system does not benefit from an increased I₂ to $[\text{NBu}_4][\text{OAc}]$ ratio, however an increased $[\text{NBu}_4][\text{OAc}]$ to I₂ ratio results in a

high yield being achieved, with the optimum being a 2:1 ratio, achieving the same result as 2.5 mol% $[\text{NBu}_4][\text{I}]$. The reaction does not work in the absence of $[\text{NBu}_4][\text{OAc}]$. A similar trend was observed by Ishihara, in a report regarding the enantioselective oxidative cycloetherification of ketophenols.⁴¹ Their system used $[\text{NBu}_4][\text{I}]$, however the authors also found that the same yields could be achieved when using iodine and tetrabutylammonium hydroxide, $[\text{NBu}_4][\text{OH}]$, with the reaction not working in absence of a tetrabutylammonium counterion. They suggested that the catalytic cycle goes *via* hypoiodite ($[\text{NBu}_4]^+[\text{IO}]^-$) or iodite ($[\text{NBu}_4]^+[\text{IO}_2]^-$) which can be generated *in situ*, by the tetrabutylammonium iodide and a co-oxidant, in our case molecular oxygen. A review article by Nachtsheim on iodine in oxidative catalysis suggested that reactions can proceed by an electrophilic I^+ species when iodine is in the presence of an external oxidant.⁴² One of the proposed I^+ species is in the form, IOAc . It is possible that in our reaction system, one of these species is formed, which explains the need for all three components, iodine, acetate counterion and molecular oxygen. It is possible that this may relate to the reoxidation of the palladium(0). Although it has been previously shown in palladium catalysis that direct reoxidation of $\text{Pd}(0)$ by molecular oxygen is achievable, this may not be possible under our reaction conditions as CO , a reductant is also present. It is known that CO can reduce $\text{Pd}(\text{II})$ to $\text{Pd}(0)$ ⁴³ and so it may be the case that these iodide species are required, as their reoxidation of $\text{Pd}(0)$ may be more kinetically competitive than that of molecular oxygen.

It was previously discussed that the major problem with the current literature regarding this reaction is the solvent choice, and gas conditions applied. The most commonly applied solvents for these reactions tend to be ethereal solvents such as 1,4-dioxane,^{25,27,29} or DMF.²⁶ Solvents are a major component in any organic reaction, and so it is important to critically evaluate the solvent choices made when optimising a catalytic system. In a solvent selection guide by a collection of some of the largest worldwide pharmaceutical companies including GlaxoSmithKline and Pfizer, it was highlighted that 1,4-dioxane is 'hazardous' and 'problematic', resulting in the need for such solvents to be avoided.⁴⁴ The review classed solvents considering their safety,

health and environmental impact. Another review on solvent selection, written solely by GlaxoSmithKline again highlighted 1,4-dioxane to have ‘major issues’.⁴⁵

It is also important to mention that when considering the safety of a reaction, ethereal solvents are almost entirely incompatible solvents for oxidation reactions. It is well established that ethereal solvents have a propensity to form explosive peroxide species when in contact with oxygen or air. This is something that is taken into consideration in both academic and industrial labs. For example, they can only be stored for short periods of time, and on re-use undergo testing for the presence of peroxide species. In the case of 1,4-dioxane, it is been shown to form peroxide species in oxidation reactions that are actually suggested to be part of the catalytic cycle. For example, Stahl and co-workers showed the decomposition of 1,4-dioxane to peroxide species to be key in the palladium catalysed C-H aryl amination of *N*-benzenesulfonyl-2-aminobiphenyl. It is believed that the *in situ* generated peroxide species can act as the oxidant within the reaction system.⁴⁶

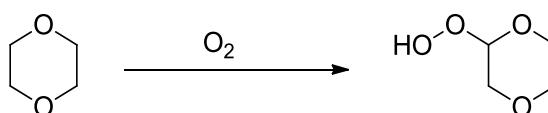


Figure 4.23 Formation of peroxide species *via* autoxidation of 1,4-dioxane.⁴⁶

In another report by Albeniz and co-workers, various solvents were tested for their ability to decompose a palladium-aryl complex to its reduced product, whereby the solvent is the H-donor.⁴⁷ Interestingly, this publication highlights the fact that sometimes when a solvent has shown to be suitable for a particular reaction, it can be immediately chosen for use in a similar one, without consideration of hazards etc. They also highlighted that this is even more problematic in reactions requiring a longer timescale. They demonstrated that the palladium-aryl complex decomposed readily in 1,4-dioxane in the presence of oxygen at 100 °C. These papers highlight the ability of ethereal solvents such as 1,4-dioxane to decompose under similar conditions to those

chosen for aminocarbonylation reactions, and so stress the importance of safe solvent selection. Whereas solvents such as 1,4-dioxane may be interesting to look at academically, it could be said that use of such solvents in oxidation reactions may terminate the possibility of these reactions being applied industrially. For this reason, we tested a variety of solvents in a bid to find a safer solvent, that could achieve as high a yield as those previously reported in 1,4-dioxane. The results can be seen in Table 4.8 shown below.

Table 4.8 Effect of solvent on catalytic performance.

2 mmol 4 mmol

Solvent	Conversion of Alkyne [%] ^a	Yield of Product [%] ^a
acetonitrile	81	53
1,4-dioxane	75	71
ethyl acetate	87	86
<i>iso</i> -propyl acetate	75	70

[a] Conversion and yield were calculated by GC using biphenyl as an internal standard. All results shown are an average of two experiments.

Pleasingly, ethyl acetate outperformed the commonly used 1,4-dioxane, with both its activity and selectivity being superior. Acetonitrile showed a high conversion of alkyne however did not give a high yield of desired product. As one of the main aims of the study was to choose a safer solvent, we also tested isopropyl acetate, as it has a higher vapour pressure than ethyl acetate and so is considered safer. Its performance was slightly sluggish compared to ethyl acetate, however was still on par with 1,4-dioxane yet dramatically safer.

We chose to use ethyl acetate for the remainder of our study, due to its high performance. Pleasingly, ethyl acetate was also classed as ‘recommended’ in the previously mentioned solvent selection guides.^{44,45}

In addition to solvent selection, the gas mixture chosen is also imperative to reaction safety, and the two factors are intrinsically linked. In the main literature examples of oxidative aminocarbonylations to date, the oxygen source has been present either as pure oxygen or air.^{25,26,27} Whereas, oxygen is undoubtedly the best terminal oxidant economically and in terms of sustainability and availability; it does come with considerable safety concerns. These hazards are easier managed on a small lab scale, however when considering industrial scale-up, gas concentrations in flammable solvents must be considered. Factors to bear in mind are the limiting oxygen concentration (LOC), and flammability limits (LFL and UFL). The LOC is the concentration of oxygen in an organic solvent, below which combustion is not possible. For ethyl acetate at 100 °C, the LOC is 9.4 vol% oxygen at a pressure of 1 bara and 9.9 vol% oxygen at a pressure of 20 bara.⁴⁸ The LFL (lower flammability limit) is the concentration of fuel vapour in air, below which combustion is not possible. As we are using carbon monoxide, a flammable gas, it is also important to consider the flammability limits. This value for carbon monoxide in air at 100 °C and atmospheric pressure is 11.5 vol%.⁴⁹ The UFL (upper flammability limit) can also be considered, and is 75 vol%, at 100 °C and atmospheric pressure. This can be considered the fuel rich region. The previously mentioned Gabriele conditions²⁵ operate in line with the UFL however in industry it is preferred to operate within the LFL limit (fuel lean conditions).⁵⁰ Firstly, this is due to a practical aspect whereby if there is a leak, or the reactor is vented (which must occur at some point) when operating under UFL conditions, it will pass through the explosion region as it intersperses with air. This would not be the case when using LFL conditions. In addition, it should be remembered that these values are stated for atmospheric pressure, and it is known that the LFL value will decrease under increased pressure, but the UFL will increase by a larger proportion.⁵¹ For this reason, we chose to operate within the LFL conditions for CO, in an attempt to improve the safety of these reactions. However, our exact reaction conditions have not been studied, and

there is a great lack in data with regards to limits at high pressures, in the presence of organic solvents. However, by combining LFL and LOC values, we hope that this should mean the reaction is safe.

At the start of the reaction optimisation process we compared gas mixtures, using palladium iodide (Table 4.1). This showed that the system is not mass transfer limited in oxygen, and so we continued to optimise the reaction system using a gas mixture of (8:92) O₂:N₂. In order to ensure, that once we changed the palladium salt to an acetate counterion, the system was still not limited, we tested the gas mixtures again. Pleasingly, the same results were obtained with air, as with (8:92) O₂:N₂ meaning that we could carry out the reaction with a more diluted gas mixture. The system was run using CO (5 bar) in (8:92) O₂:N₂ (30 bar) to give a total reaction pressure of 35 bar. This fits as closely as possible with the LOC and LFL whereby both values should fall within the limits, however as highlighted by Stahl and co-workers, little experimental evidence exists that takes into consideration solvents at all reaction temperatures, with diluted gas mixtures and organic products.⁴⁸ This means that it is impossible to explicitly state the safety of the reaction, however these conditions are undoubtedly safer than those reported in previous oxidative carbonylation literature.

We also examined some additional reaction parameters including reaction temperature, addition of base, and running the reaction without a glass liner in the reactor body. The results can be seen in Table 4.9.

Table 4.9 Comparison of reaction system parameters.

$\text{Ph}-\text{C}\equiv\text{CH}$ (2 mmol) + $\text{CH}_3\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)\text{H}$ (4 mmol)
 $\xrightarrow[\text{CO (5 bar), 8\% O}_2/\text{N}_2 \text{ (30 bar)}]{\text{Pd(OAc)}_2 \text{ (0.2 mol\%)}, [\text{NBu}_4][\text{I}] \text{ (2.5 mol\%)}, \text{EtOAc (4 mL), X }^\circ\text{C, 6 h}}$
 $\text{Ph}-\text{C}\equiv\text{C}-\text{C}(=\text{O})-\text{N}(\text{CH}_2\text{CH}_3)_2$

Entry	Base ^b	Temp. [°C]	Conv. alkyne [%] ^a	Yield of product [%] ^a
1	/	80	87	86
2 ^c	/	80	98	78
3	K ₃ PO ₄	80	35	32
4	/	60	44	43
5	/	100	90	84
6 ^d	/	80	93	83

[a] Conversion and yield were determined by GC using biphenyl as internal standard

[b] 2 equivalents of base were added

[c] Reaction was run in Hasselhoff reactor without a glass liner

[d] Reaction run for 16 h

All results shown are an average of 2 experiments

We chose to test the addition of caesium carbonate and potassium phosphate as these bases had previously been shown to have an enhancing effect on oxidative carbonylation. Xia and co-workers showed caesium carbonate to give a better result than sodium methoxide or potassium *tert*-butoxide. However their best result was achieved with potassium phosphate.²⁷ Under our reaction conditions, the addition of base decreased the yield; and so we continued the reaction optimisation in absence of base.

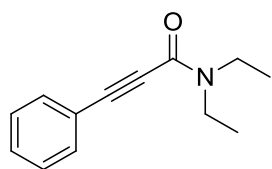
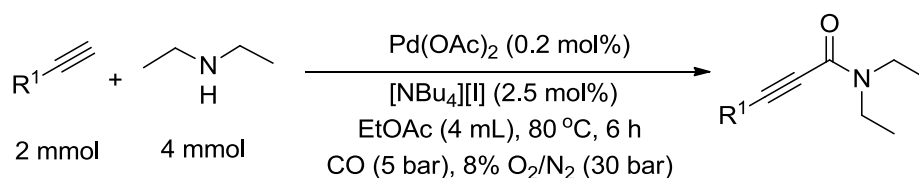
With regards to reaction temperature, both 60 °C and 100 °C were tested. It was observed that the reaction was slower at 60 °C; and at 100 °C had an increase in alkyne conversion but the selectivity decreased. This suggests the reaction is more erratic at high temperature, thus causing an increase in side reactions. For this reason we chose to use 80 °C.

All of the reaction optimisation was carried out in 35 mL Hastelloy reactors fitted with a glass liner. This was done in order to ensure that the reaction was

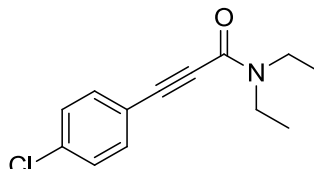
not catalysed by the metals present in the reactor body. However, we carried out a control reaction to see if this did occur, and in fact found the opposite whereby the yield and selectivity were decreased by loss of the glass liner. It is possible that the carbon monoxide gas reacts in some way with the reactor body, causing the promotion of a side reaction. This would explain the increase in alkyne conversion, yet the overall decrease in reaction yield.

We also noted that an increase in reaction time from 6 hours to 16 hours again led to an increase in alkyne conversion, yet the same yield of desired product, indicating that the reaction is finished after 6 hours. A reaction time of 6 hours was chosen for the remainder of the study.

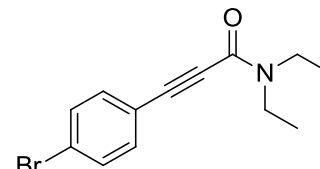
Once the reaction conditions had been fully optimised we wished to carry out a substrate scope. The substrate scope performed was smaller than the previous 2-alkynoate scope (Chapter 3) as this was not the main focus of the study. We felt that the scope of the reaction was not a major problem with the current literature, and so we simply desired to test if our safer reaction conditions could demonstrate the same wide substrate applicability as those reported previously. We began by testing a variety of alkynes, using diethylamine. The results can be seen in Figure 4.24.



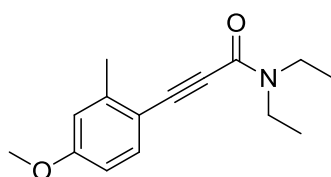
1 81%



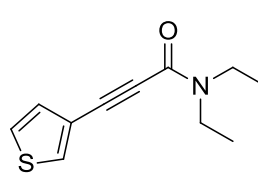
2 75%



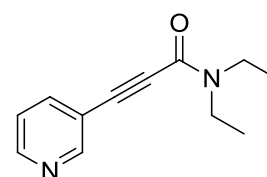
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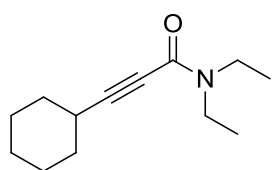
4 92%



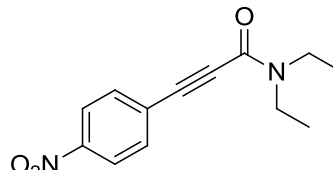
5 84%



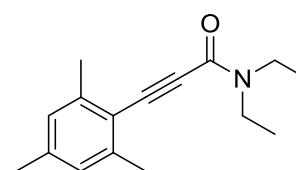
6 77%



7 52 %



8 65%



9 75%

All yields shown are isolated yields

Figure 4.24 Alkyne substrate scope with optimised conditions.

As shown, it was possible to use both activated and unactivated alkynes. Electron donating **4** and electron withdrawing groups **2,3,8** could be used to achieve fair to good yields. Little difference was observed between electron donating and electron withdrawing substituents; this would suggest that the addition of the alkyne to the Pd is not the rate determining step. This indifference has been observed previously by both Gabriele²⁵ and Xia.²⁷ The system also showed to be heteroatom tolerant, as can be seen with **5** and **6**. The system could also be used with sterically hindered alkynes, such as 2-ethynyl-1,3,5-trimethylbenzene **9**. In terms of yield, the isolated yields are competitive with those previously reported in the literature. In the case of Xia

and co-workers, they can achieve slightly higher yields in some cases, however this system requires a five times greater catalyst loading. This is also the first demonstration of using 3-ethynylpyridine or 3-ethynylthiophene. Interestingly, Gabriele and co-workers did also note a lower than expected yield with *p*-nitrophenylacetylene. They demonstrated a high conversion of 100%, however an isolated yield of only 28%. This was attributed to a competing reaction whereby the alkyne undergoes addition of the amine to form (E)-diethyl-[2-(4-nitrophenyl)vinyl]amine. (Figure 4.25)

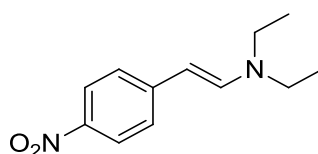


Figure 4.25 Side product formation with *p*-nitrophenylacetylene.²⁵

We did test 4-cyanophenylacetylene also, however it gave only a 14% yield of the desired product. This also proved to be a problematic substrate for Xia and co-workers.²⁷ It has been shown previously that alkynes containing nitrile groups can undergo Pd(II) catalysed cyclisation reactions (Figure 4.26).²⁸ The conditions reported by Zhao and Lu are very similar to our optimised reaction conditions, which demonstrates that nitriles can undergo other reactions with alkynes in the presence of palladium. Whereas this may not be the exact side reaction occurring here, it is probable that other side reactions are to blame for the poor yield obtained with this substrate.

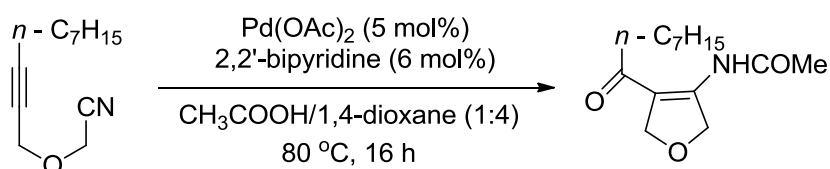
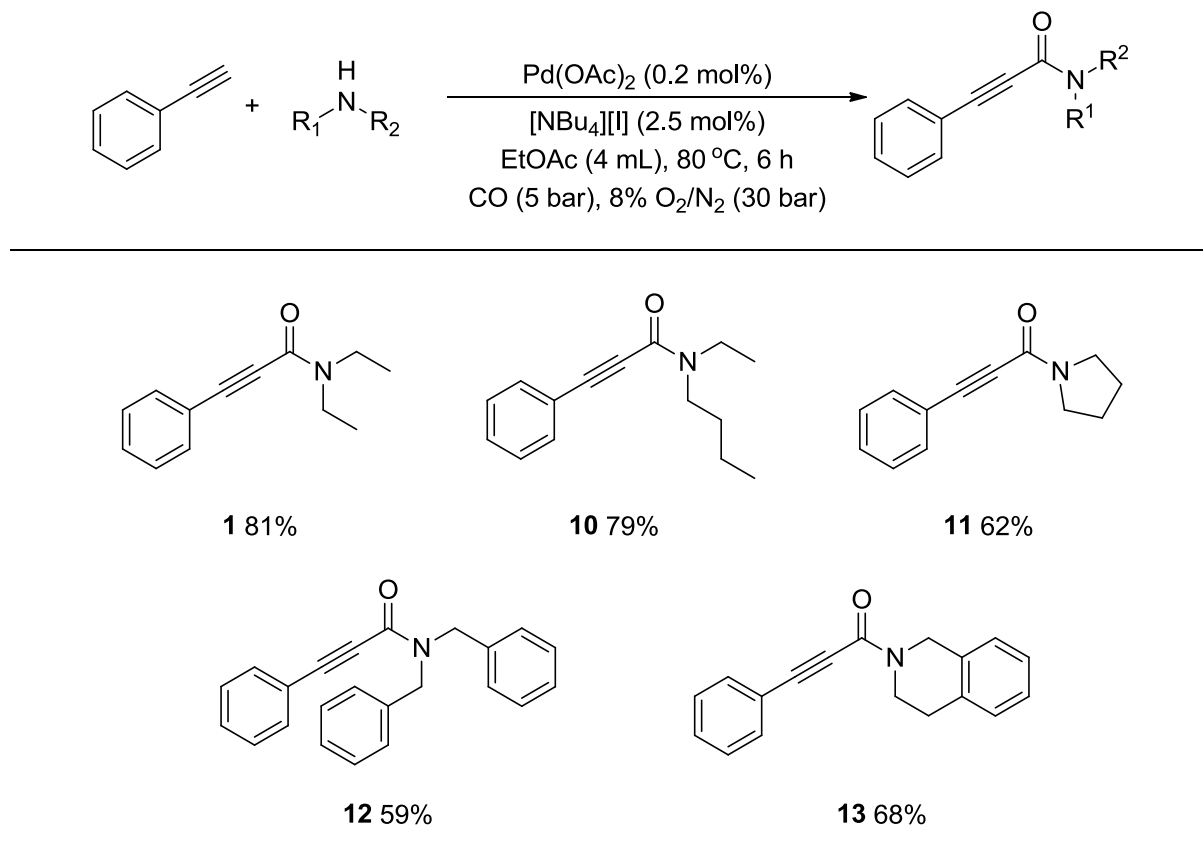


Figure 4.26 Pd(II) catalysed cyclisation reaction in the presence of nitrile group.²⁸

After testing various alkynes, we also tried a variety of secondary amines. It was observed that both aromatic and aliphatic amines performed well.

Unsymmetrical amines such as **10** and **13** gave fair yields. Unlike that found by Gabriele and co-workers, sterically hindered amines such as **12** also gave a fair yield.²⁵ The results can be seen in Figure 4.27.



All yields shown are isolated yields

Figure 4.27 Amine substrate scope with optimised conditions.

We did attempt to use tributylamine, however the reaction was unsuccessful. Recently Bhanage and co-workers reported a system for the oxidative *N*-dealkylation/ carbonylation of tertiary amines to give 2-ynamides.³⁰ The system worked well with symmetrical tertiary amines such as tributylamine, however when unsymmetrical amines were used, a mixture of products was observed.

In a similar manner to the oxidative carbonylation of alkynes and alcohols, the mechanism for the synthesis of 2-ynamides has not been studied in such detail as what would be observed with palladium(II) catalysed alcohol oxidation for example. Mechanisms have been suggested by Gabriele²⁵ and Xia²⁷ however little experimental evidence, with the exception of mass spectrometry²⁷ exists to support the postulated mechanism.

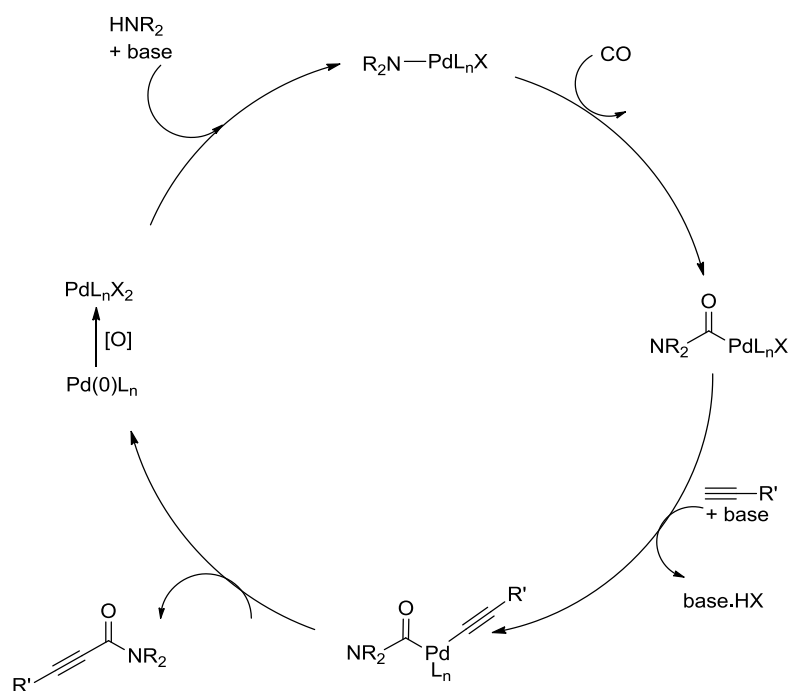


Figure 4.28 Mechanism suggested by Xia and co-workers.²⁷

Further detailed mechanistic studies, including reaction kinetics, Hammett plots and kinetic isotope effects should be performed to aid the understanding of this complex reaction system. Understanding of the reaction mechanism is a crucial factor in enhancing the design of second generation catalysts.

The palladium catalyst loading in the reported system (0.2 mol%) is similar to that reported previously by Gabriele and co-workers.²⁵ However, as with the 2-alkynoate system discussed in Chapter 3, this method could still be improved by the ability to recycle the palladium catalyst. Recycling palladium can be problematic due to its propensity to form inactive palladium black however this is a challenge to be considered for future work in order to further improve the sustainability of the reaction system.

4.4 Conclusion

In conclusion, a system has been developed that allows for the synthesis of 2-ynamides *via* oxidative carbonylation. The method does not require the use of ligands, and can achieve high yields with low palladium loadings. In addition, the main aims of the study have been met, whereby a recommended, greener solvent, ethyl acetate can be used in replacement of hazardous solvents such as 1,4-dioxane. Oxygen has also been applied as the terminal oxidant, and can be operated under safer conditions than those reported in previous literature. Finally, the optimised reaction conditions can be used for oxidative carbonylation with a variety of alkynes and secondary amines. Future work would include a mechanistic study to further understand the role of $[\text{NBu}_4][\text{I}]$ and to study the kinetics of the reaction.

4.5 Experimental

4.5.1 General Considerations

Unless otherwise stated, all reagents were purchased from Sigma-Aldrich and used without further purification. The following chemicals were purchased from Fluorochem: 4-chlorophenylacetylene, 4-bromophenylacetylene, 4-cyanophenylacetylene, ethynylcyclohexane, 1-ethynyl-4-nitrobenzene, and palladium(II) acetate (99%). The following chemicals were purchased from Alfa Aesar: palladium(II) trifluoroacetate (97%), palladium(II) trimethylacetate (97%) and dibenzylamine. The following palladium salts were purchased from Sigma Aldrich: palladium(II) propionate ($\geq 99.5\%$), palladium(II) acetate (≥ 99.9 trace metal basis), palladium(II) chloride ($\geq 99.9\%$), palladium(II) iodide ($\geq 99.9\%$). Carbon monoxide (CP Grade), air and O₂ cylinders were from BOC and pre-mixed O₂:N₂(8:92) (β standard) cylinder was from BOC Special Gases.

All synthesis and reactions were carried out in oven-dried glassware. Any reactions that were monitored by thin layer chromatography were carried out using Merck silica gel 60 sheets and visualised with UV light. Flash column chromatography was performed with 60 Å silica gel as the stationary phase, and all solvents used were of analytical grade.

¹H-NMR spectra were recorded on a Bruker AVX400 (400 MHz) spectrometer at room temperature. ¹³C NMR spectra were recorded on a Bruker AVX400 (101 MHz) spectrometer at room temperature. NMR data is reported as follows; chemical shift is recorded in parts per million (δ , ppm) in deuterated chloroform (CDCl₃) taken as 7.26 ppm. Multiplicity; s= singlet, d=doublet, dd= doublet of doublets, td= triplet of doublets, dt = doublet of triplets, m= multiplet.

Melting points were measured on Stuart melting point apparatus (Digital, SMP10). IR spectra were measured on PerkinElmer Spectrum 100 FT-IR Spectrometers. Mass spectra were recorded a Waters Micromass LCT Premier spectrometer.

Analysis by Gas Chromatography was performed using an Agilent 6890N series gas chromatograph. An Agilent 19091J-433 HP-5 5% Phenyl Methyl Siloxane capillary (column) (30.0 m x 250 µm x 0.25 µm nominal) was employed for all the separations using the following conditions. Column head pressure, 30 kPa (4.49 psi) helium; initial column temperature, 40 °C; initial hold time, 0 min; rate of temperature ramp 1, 4 °C/min; next temperature, 100 °C; hold time, 0 min; rate of temperature ramp 2, 30 °C/min, final temperature 320 °C; hold time, 15 min; injection temperature, 250 °C; detection temperature, 250 °C. The effluent was combusted in a H₂/Air flame and detected using an FID (flame ionisation detector). Ion count data were sent to a plotter, which integrated the area under the peaks.

The conversions and yields reported were calculated by GC using biphenyl as an internal standard. An initial response factor (R_f) was calculated for the particular product or starting material, by dissolving a known amount of analyte and standard (biphenyl) in ether. Then the following equation was used to calculate the R_f value:

$$R_f = \frac{\text{Moles}_{\text{analyte}} \times \text{Area}_{\text{internal standard}}}{\text{Moles}_{\text{internal standard}} \times \text{Area}_{\text{analyte}}}$$

The amount of product or starting material present was then calculated using the following equation:

$$\text{Moles}_{\text{analyte}} = \frac{\text{Moles}_{\text{internal standard}} \times R_f \times \text{Area}_{\text{analyte}}}{\text{Area}_{\text{internal standard}}}$$

4.5.2 Safety Considerations

This work requires the use of carbon monoxide. Only trained personnel should be allowed to work with carbon monoxide cylinders. Carbon monoxide is a toxic, flammable gas. The cylinder was kept in a ventilated fume cupboard, fitted with a CO alarm. All tubing and reaction vessels were vented in the fume

cupboard. These reactions also use high pressures of air or O₂:N₂ (8:92). All reactions were carried out at pressures significantly under the pressure ratings of the reactor vessels. The reactor vessels were also fitted with safety relief valves in case of unprecedented pressure build up.

4.5.3 General Methods

General Considerations

Pd(OAc)₂ which was ≥99.9% trace metal basis purity (from Sigma Aldrich) was used and it was found that lower grades of Pd(OAc)₂ led to reduced yields. Pd(OAc)₂ was added to the reactions *via* stock solution which were only kept for a maximum of three days.

All reactions were carried out in 45 mL pressure vessels which were placed inside a pre-heated aluminium block, on a stirring hotplate. The heating block was thermostatically controlled during the reaction. Unless otherwise stated, all reactions were carried out in a glass liner, with a Teflon coated triangular stir bar.

Optimisation of Catalytic System

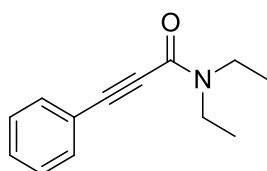
Reactions were performed in 45 mL high-pressure reactors made of hastelloy and the reaction mixture was placed in a glass liner, equipped with a magnetic stirrer. To the glass liner, tetrabutylammonium iodide (2.5 mol%, 0.05 mmol, 0.0185 g) and Pd(OAc)₂ (0.2 mol%, 0.004 mmol, 0.0009 g) from a stock solution in ethyl acetate (4 mL) were added. This was followed by the addition of alkyne (2 mmol) and amine (4 mmol). The glass liner was placed in a reactor and then pressurized with 5 bar of carbon monoxide gas, followed by O₂:N₂ (8:92) to give a total reaction pressure of 35 bar. The reactor was then stirred (600 rpm) on a pre-heated heating block at 80 °C for six hours. Once the reaction was complete, the reactor was cooled in an ice bath and slowly depressurised in a fume hood. Internal standard (biphenyl) (~0.2 g) was added, and the glass liner magnetically stirred for 1 minute to ensure all standard was fully dissolved. A sample was then prepared for GC analysis by

filtration through a silica plug with diethyl ether to remove any catalyst components. The sample was then submitted for GC analysis.

Preparation of Isolated Substrates

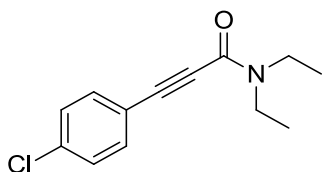
Procedure was the same as described above, however at the end of the reaction the reactor was cooled and depressurized, then poured into a separating funnel and brine added. The aqueous layer was then separated and back extracted with ethyl acetate twice. The combined organic layers were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography, and the appropriate fractions combined and concentrated under reduced pressure. The product was then dried under high vacuum.

4.5.4 Product Characterisation



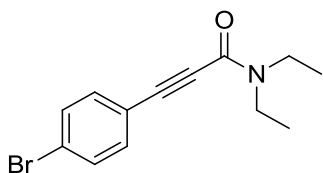
***N, N*-diethyl-3-phenylpropiolamide (1)**

Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 2:1) to afford **1** as a golden orange oil (0.3325 g, 81 %). ¹H NMR (400 MHz, CDCl₃): δ 7.47-7.44 (m, 2H), 7.35-7.25 (m, 3H), 3.62-3.55 (q, *J* = 7.1 Hz, 2H), 3.43-3.36 (q, *J* = 7.1 Hz, 2H), 1.23-1.17 (t, *J* = 7.1 Hz, 3H), 1.12-1.07 (t, *J* = 7.15 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 154.3, 132.7, 130.2, 128.9, 121.1, 89.3, 82.3, 44.0, 39.7, 14.8, 13.2. HRMS (ESI⁺) Calc. for C₂₆H₃₁N₂O₂ [2M+H⁺] 403.2386, found: 403.2384. IR (neat): 2988, 2225, 1617, 1424, 1286, 1136, 757, 689 cm⁻¹. Analytical data was in correspondence with literature data.²⁰



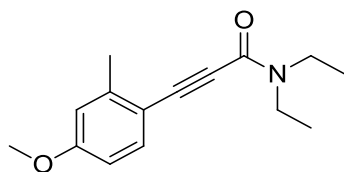
3-(4-chlorophenyl)-*N,N*-diethylpropiolamide (**2**)

Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 7:3) to afford **2** as an orange crystalline solid (0.3560 g, 75 %). ¹H NMR (400 MHz, CDCl₃): δ 7.48-7.44 (m, 2H), 7.36-7.32 (m, 2H), 3.68-3.61 (q, *J* = 7.2 Hz, 2H), 3.51-3.44 (q, *J* = 7.2 Hz, 2H), 1.30-1.25 (t, *J* = 7.2 Hz, 3H), 1.21-1.16 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 153.9, 136.3, 133.7, 129.1, 119.4, 87.9, 82.9, 43.7, 39.5, 14.6, 13.0. HRMS (ESI⁺) Calc. for C₂₆H₂₉N₂O₂Cl₂ [2M+H⁺] 471.1606, found: 471.1625. m.p. 71 °C. IR (neat): 2991, 2217, 1610, 1430, 1298, 1088, 840, 733 cm⁻¹. Analytical data was in correspondence with literature data.²⁰



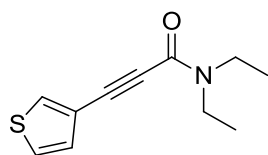
3-(4-bromophenyl)-*N,N*-diethylpropiolamide (**3**)

Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 2:1) to afford **3** as a light brown solid (0.4499 g, 81 %). ¹H NMR (400 MHz, CDCl₃): δ 7.53 -7.49 (m, 2H), 7.41-7.37 (m, 2H), 3.68-3.61 (q, *J* = 7.2 Hz, 2H), 3.51-3.44 (q, *J* = 7.2 Hz, 2H), 1.31-1.24 (t, *J* = 7.2 Hz, 3H), 1.21-1.15 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 153.9, 133.8, 132.0, 124.1, 119.8, 87.9, 83.0, 43.7, 39.5, 14.6, 13.0. HRMS (ESI⁺) Calc. for C₁₃H₁₅NOBr [M+H⁺] 280.0337, found: 280.0333. m.p. 93-94 °C. IR (neat): 2995, 2217, 1611, 1431, 1292, 1008, 836, 733 cm⁻¹. Analytical data was in correspondence with literature data.²⁰



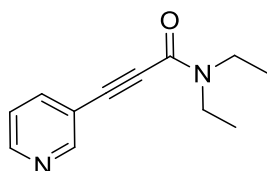
***N,N*-diethyl-3-(4-methoxy-2-methylphenyl)propiolamide (4)**

Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 3:2) to afford **4** as an orange crystalline solid (0.4525 g, 92 %). ¹H NMR (400 MHz, CDCl₃): δ 7.48-7.44 (d, *J* = 8.5 Hz, 1H), 6.77-6.74 (m, 1H), 6.73-6.69 (m, 1H), 3.83-3.80 (s, 3H), 3.70-3.64 (q, *J* = 7.2 Hz, 2H), 3.51-3.45 (q, *J* = 7.2 Hz, 2H), 2.46-2.45 (s, 3H), 1.30-1.26 (t, *J* = 7.2 Hz, 3H), 1.21-1.16 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 160.9, 154.5, 143.4, 134.8, 115.4, 112.9, 111.7, 88.7, 85.1, 55.4, 43.7, 39.4, 21.1, 14.6, 13.1. HRMS (ESI⁺) Calc. for C₃₀H₃₉N₂O₄ [2M+H⁺] 491.2910, found: 491.2912. m.p. 40-41 °C. IR (neat): 2980, 2214, 1606, 1425, 1289, 1248, 1113, 865, 730 cm⁻¹.



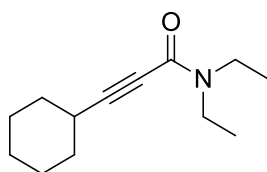
***N,N*-diethyl-3-(thiophen-3-yl)propiolamide (5)**

Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 3:2) to afford **5** as a golden oil (0.3667 g, 84 %). ¹H NMR (400 MHz, CDCl₃): δ 7.66-7.62 (d, *J* = 1.7 Hz, 1H), 7.33-7.29 (dd, *J* = 3.2, 4.7 Hz, 1H), 7.21-7.17 (d, *J* = 4.1 Hz, 1H), 3.70-3.60 (q, *J* = 7.1 Hz, 2H), 3.51-3.42 (q, *J* = 7.1 Hz, 2H), 1.31-1.23 (t, *J* = 7.1 Hz, 3H), 1.21-1.13 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 154.1, 131.9, 130.1, 126.0, 120.1, 84.6, 82.0, 43.7, 39.4, 14.5, 13.0. HRMS (ESI⁺) Calc. for C₂₂H₂₇N₂O₂S₂ [2M+H⁺] 415.1514, found: 415.1524. IR (neat): 3092, 2980, 2221, 1611, 1428, 1277, 1130, 784, 626 cm⁻¹.



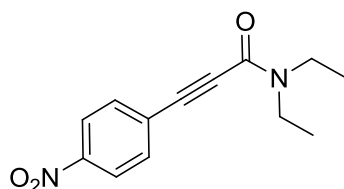
***N,N*-diethyl-3-(pyridin-3-yl)propiolamide (6)**

Purified by flash column chromatography (0.1 % Et₃N in ethyl acetate / hexane 3:1) to afford **6** as a yellow oil (0.3051 g, 77 %). ¹H NMR (400 MHz, CDCl₃): δ 8.78-8.73 (m, 1H), 8.65-8.60 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.86-7.81 (m, 1H), 7.34-7.29 (m, 1H), 3.70-3.62 (q, *J* = 7.2 Hz, 2H), 3.53-3.45 (q, *J* = 7.2 Hz, 2H), 1.32-1.27 (t, *J* = 7.2 Hz, 3H), 1.22-1.15 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 153.5, 152.8, 150.2, 139.4, 123.3, 118.2, 85.6, 85.0, 43.8, 39.5, 14.6, 13.0. HRMS (ESI⁺) Calc. for C₃₆H₄₂N₆O₃Na [3M+Na⁺] 629.3216, found: 629.3199. IR (neat): 2987, 2221, 1615, 1428, 1289, 1140, 703, 580 cm⁻¹. Analytical data was in correspondence with literature data.²⁰



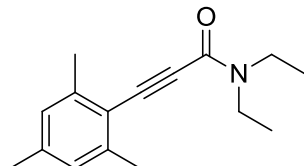
3-cyclohexyl-*N,N*-diethylpropiolamide (7)

Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 3:1) to afford **7** as a golden oil (0.2201 g, 52 %). ¹H NMR (400 MHz, CDCl₃): δ 3.61-3.54 (q, *J* = 7.1 Hz, 2H), 3.45-3.37 (q, *J* = 7.2 Hz, 2H), 2.60-2.51 (m, 1H), 1.87-1.78 (m, 2H), 1.76-1.66 (m, 2H), 1.58-1.46 (m, 3H), 1.41-1.28 (m, 3H), 1.24-1.17 (t, *J* = 7.1 Hz, 3H), 1.15-1.10 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 154.4, 95.3, 74.4, 43.6, 39.2, 31.8, 29.1, 25.8, 24.7, 14.3, 13.0. HRMS (ESI⁺) Calc. for C₂₆H₄₃N₂O₂ [2M+H⁺] 415.3324, found: 415.3314. IR (neat): 2930, 2232, 1621, 1423, 1275, 1222, 1170, 1087, 894, 737 cm⁻¹.



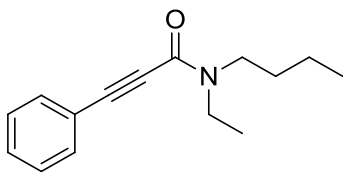
***N,N*-diethyl-3-(4-nitrophenyl)propiolamide (8)**

Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 3:2) to afford **8** as a dark red crystalline solid (0.3158 g, 65 %). ¹H NMR (400 MHz, CDCl₃): 8.26-8.21 (m, 2H), 7.72-7.66 (m, 2H), 3.70-3.63 (q, *J* = 7.2 Hz, 2H), 3.53-3.46 (q, *J* = 7.2 Hz, 2H), 1.33-1.26 (t, *J* = 7.2 Hz, 3H), 1.22-1.18 (m, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 153.2, 148.7, 133.2, 127.6, 125.7, 124.1, 123.9, 86.4, 86.1, 43.8, 39.6, 14.6, 12.9. m.p. 90 °C. HRMS (ESI⁺) Calc. for C₂₆H₂₉N₄O₆ [2M+H⁺] 493.2087, found: 493.2069. IR (neat): 3034, 2221, 1623, 1420, 1191, 755, 690 cm⁻¹. Analytical data was in correspondence with literature data.²⁵



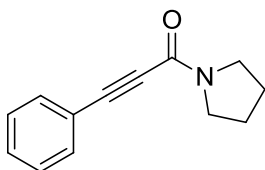
***N,N*-diethyl-3-mesitylpropiolamide (9)**

Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 3:1) to afford **9** as a golden oil (0.3654 g, 75 %). ¹H NMR (400 MHz, CDCl₃): δ 6.91-6.85 (s, 2H), 3.74-3.62 (q, *J* = 7.1 Hz, 2H), 3.52-3.43 (q, *J* = 7.1 Hz, 2H), 2.47-2.40 (s, 6H), 2.32-2.24 (s, 3H), 1.30-1.24 (t, *J* = 7.1 Hz, 3H), 1.22-1.16 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 154.4, 141.6, 139.8, 128.2, 127.9, 117.7, 89.7, 87.4, 43.6, 39.4, 21.5, 21.0, 14.6, 13.0. HRMS (ESI⁺) Calc. for C₃₂H₄₃N₂O₂ [2M+H⁺] 487.3325, found: 487.3336. IR (neat): 2984, 2206, 1621, 1417, 1280, 1128, 852, 733 cm⁻¹.



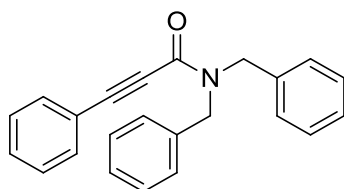
***N*-butyl-*N*-ethyl-3-phenylpropiolamide (10)**

Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 3:1) to afford **10** as a golden yellow oil (0.3609 g, 79%). ¹H NMR (400 MHz, CDCl₃): δ 7.56-7.50 (m, 2H), 7.44-7.32(m, 3H), 3.70-3.58 (m, 2H), 3.50-3.39 (m, 2H), 1.69-1.53 (m, 2H), 1.46-1.31 (m, 2H), 1.30-1.15 (m, 3H), 1.10-0.92 (m, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 154.3, 132.4, 130.0, 128.6, 121.0, 89.2, 89.1, 82.3, 82.1, 48.8, 44.0, 39.8, 31.2, 29.9, 20.3, 20.1, 14.4, 14.0, 12.8. Additional peaks in the carbon NMR are attributed to the presence of rotamers. HRMS (ESI⁺) Calc. for C₃₀H₃₈N₂O₂Na [2M+Na⁺] 481.2831, found: 481.2820. IR (neat): 2966, 2225, 1620, 1423, 1293, 1137, 757, 689 cm⁻¹.



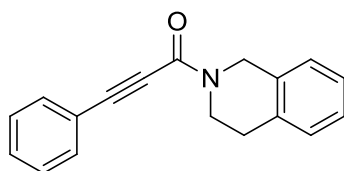
3-phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-one (11)

Purified by flash column chromatography (hexane / ethyl acetate 1:1) to afford **11** as a dark orange solid (0.2481 g, 62 %). ¹H NMR (400 MHz, CDCl₃): δ 7.56-7.52 (m, 2H), 7.44-7.33 (m, 3H), 3.77-3.70 (m, 2H), 3.56-3.51 (m, 2H), 2.00-1.93 (m, 4H). ¹³C NMR (101 MHz, CDCl₃): δ 152.9, 132.6, 130.1, 128.6, 120.8, 88.8, 82.8, 48.3, 45.5, 25.6, 24.9. m.p. 65 °C. HRMS (ESI⁺) Calc. for C₂₆H₂₆N₂O₂Na [2M+Na⁺] 421.1892, found: 421.1879. IR (neat): 2980, 2221, 1621, 1487, 1416, 1189, 760, 690 cm⁻¹. Analytical data was in correspondence with literature data.³⁰



***N,N*-dibenzyl-3-phenylpropiolamide (**12**)**

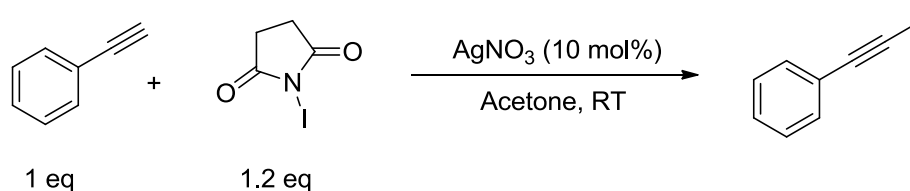
Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 10:1) to afford **12** as an orange solid (0.4001 g, 59 %). ¹H NMR (400 MHz, CDCl₃): δ 7.52 -7.48 (m, 2H), 7.43 -7.26 (m, 13H), 4.78-4.74 (s, 2H), 4.58-4.55 (s, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 155.2, 136.4, 136.2, 132.6, 130.3, 129.0, 128.9, 128.7, 128.6, 128.1, 127.9, 127.8, 120.5, 91.0, 81.8, 51.6, 46.5. m.p. 104 °C. HRMS (ESI⁺) Calc. for C₂₃H₂₀NO [M+H⁺] 326.1545, found: 326.1536. IR (neat): 3024, 2214, 1621, 1449, 1192, 754, 690, 561 cm⁻¹.



1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-phenylprop-2-yn-1-one (13**)**

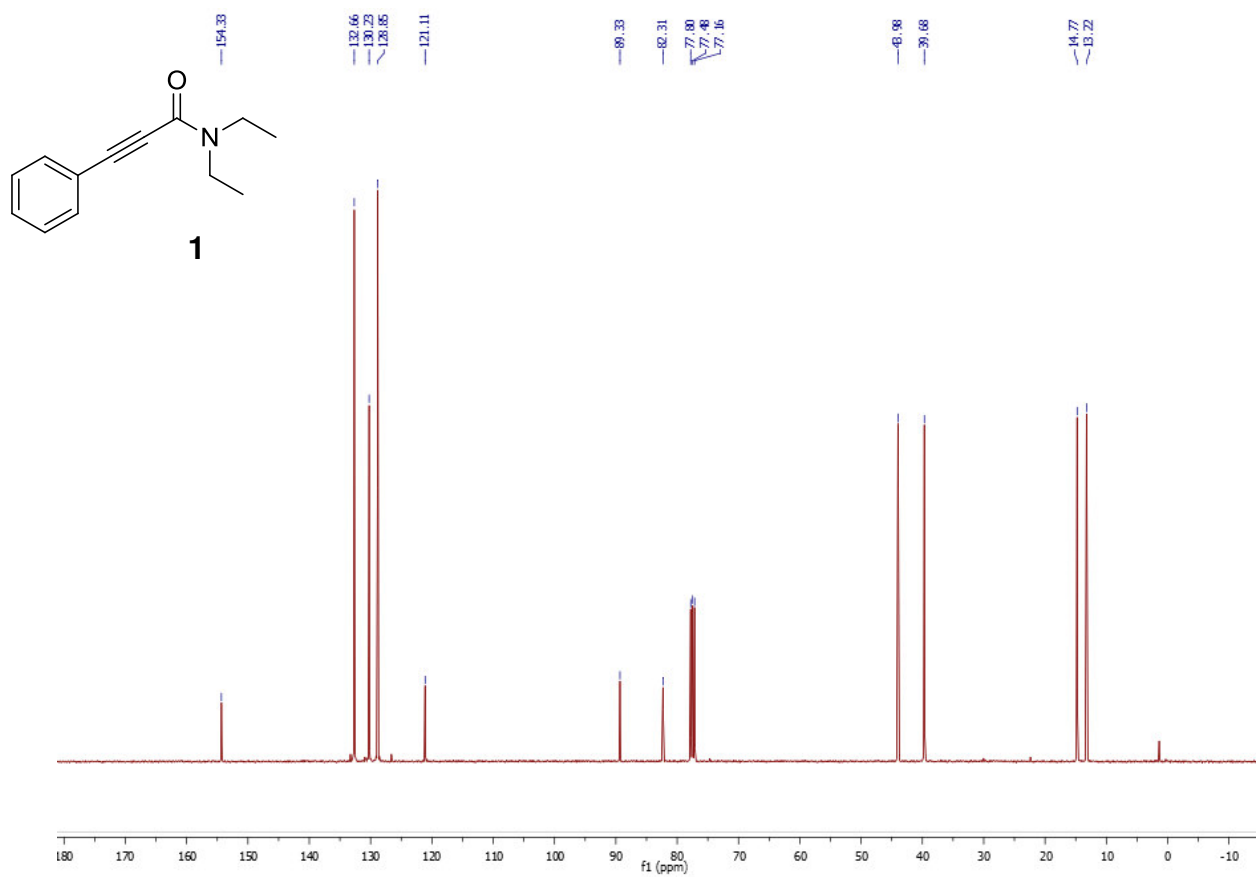
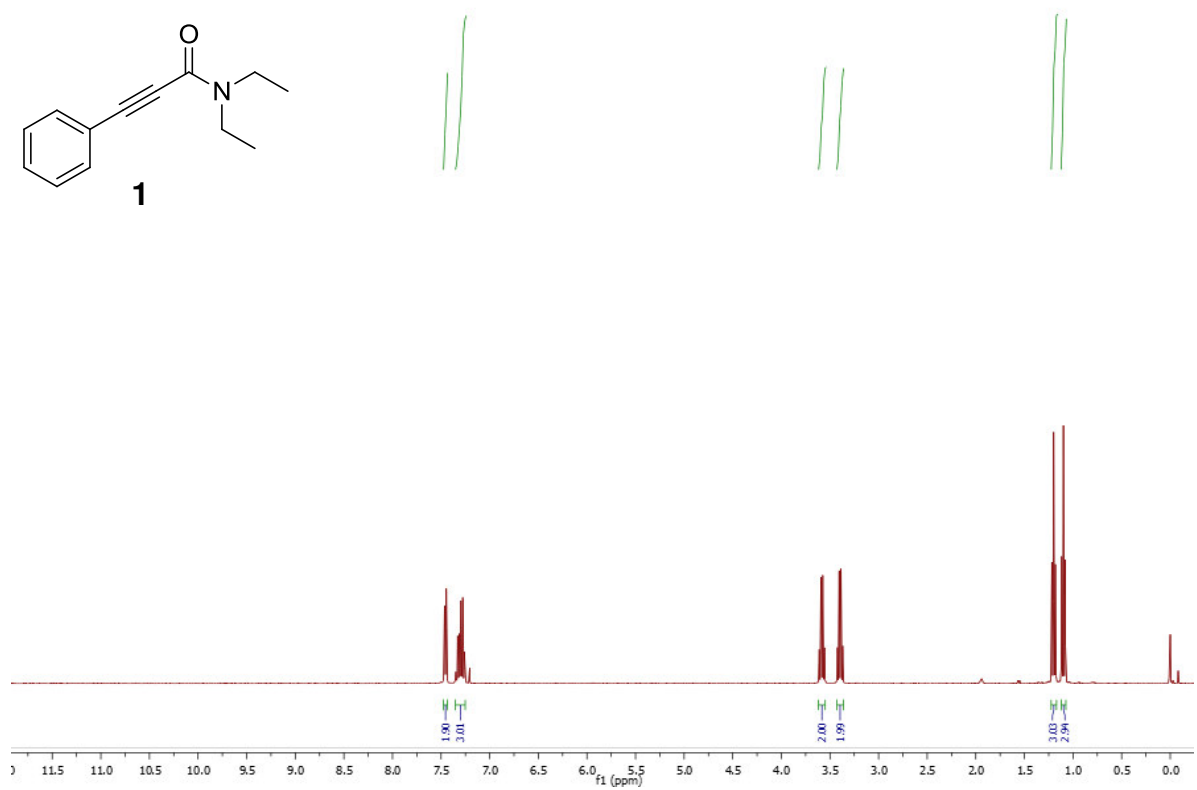
Purified by flash column chromatography (0.1 % Et₃N in hexane / ethyl acetate 7:3) to afford **13** as a light brown solid (0.3535 g, 68 %). ¹H NMR (400 MHz, CDCl₃): δ 7.61-7.55 (d, *J*=7.8 Hz, 2H), 7.46-7.35 (m, 3H), 7.25-7.13 (m, 4H), 5.01-4.78 (m, 2H), 4.10-3.88 (m, 2H), 3.01-2.88 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 153.8, 153.5, 134.7, 134.0, 132.5, 132.4, 130.2, 129.1, 128.8, 128.7, 127.2, 126.9, 126.8, 126.7, 126.3, 120.6, 91.2, 90.5, 81.6, 81.5, 48.8, 44.8, 44.2, 39.8, 29.7, 28.5. Additional peaks in the carbon NMR are attributed to the presence of rotamers. m.p. 72-73 °C. HRMS (ESI⁺) Calc. for C₁₈H₁₅NONa [M+Na⁺] 284.1051, found: 284.1038. IR (neat): 3066, 2904, 2850, 2225, 1619, 1435, 1193, 741, 691 cm⁻¹. Analytical data was in correspondence with literature data.¹⁹

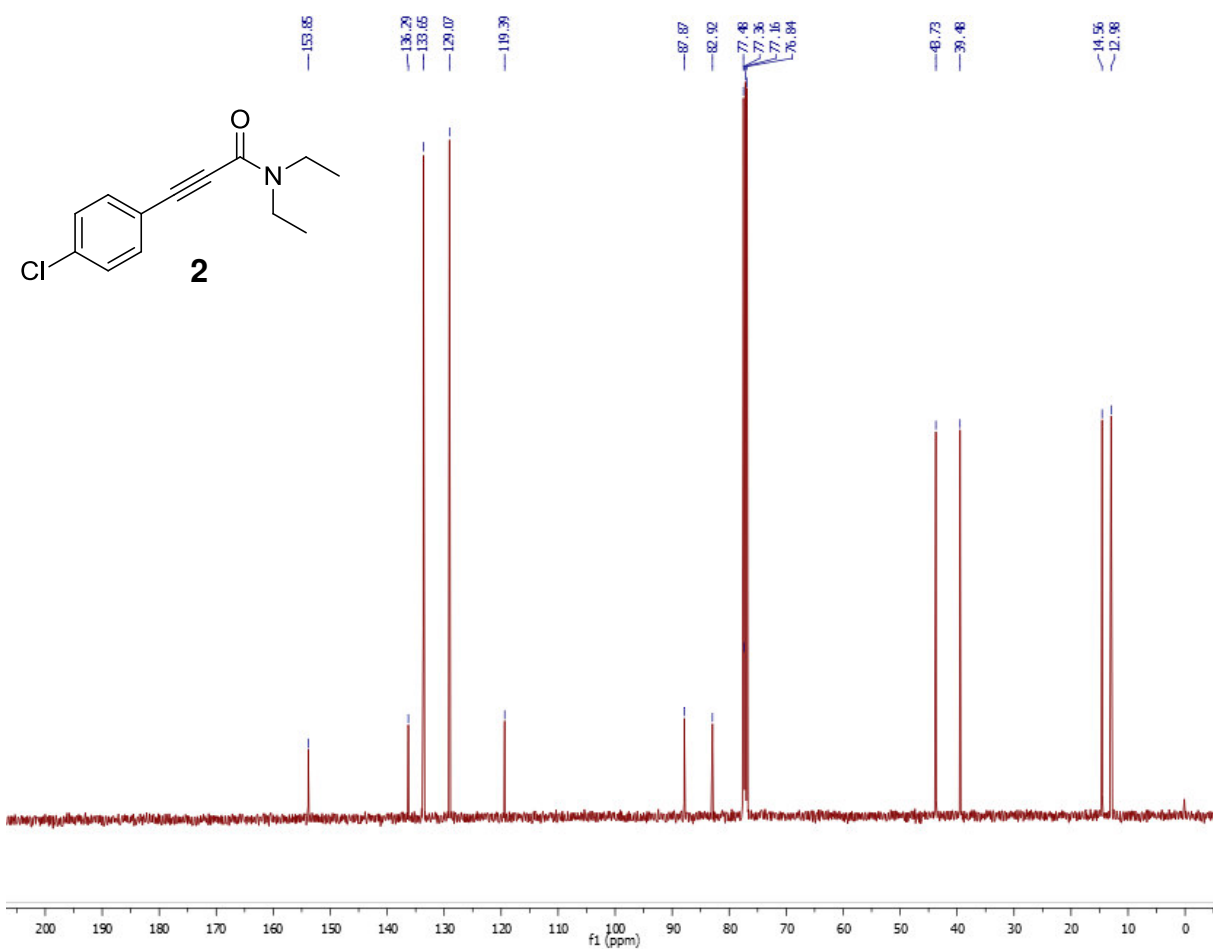
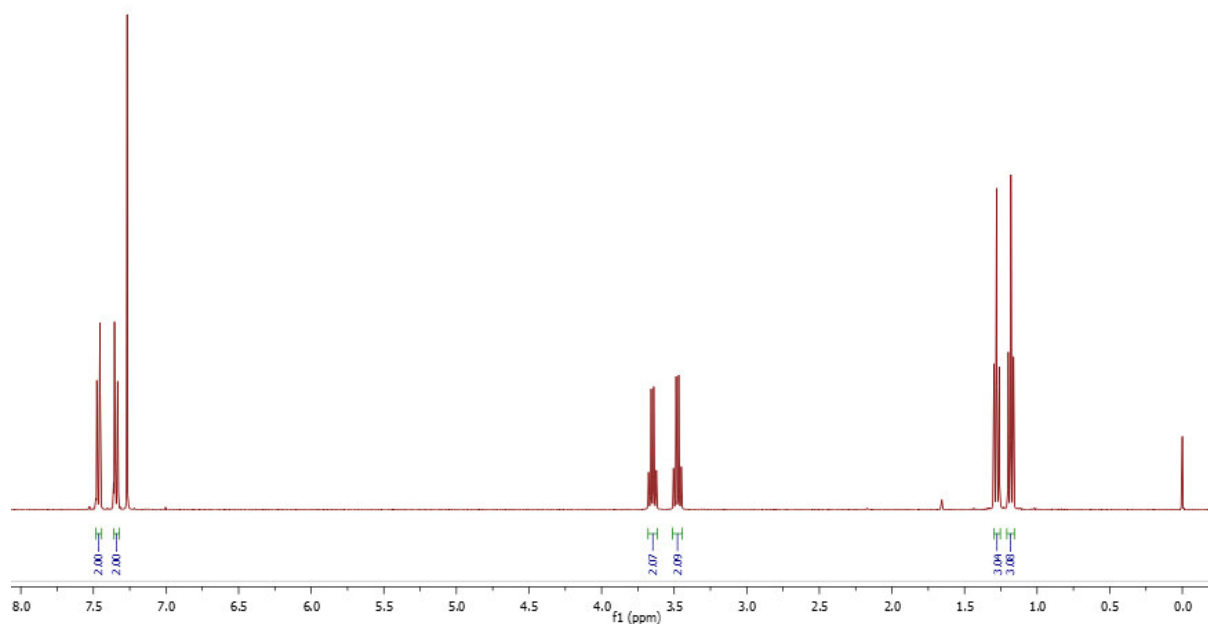
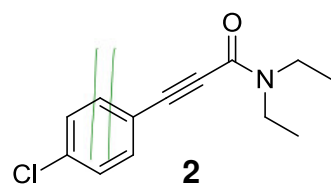
4.5.5 Synthesis of Iodoethynylbenzene

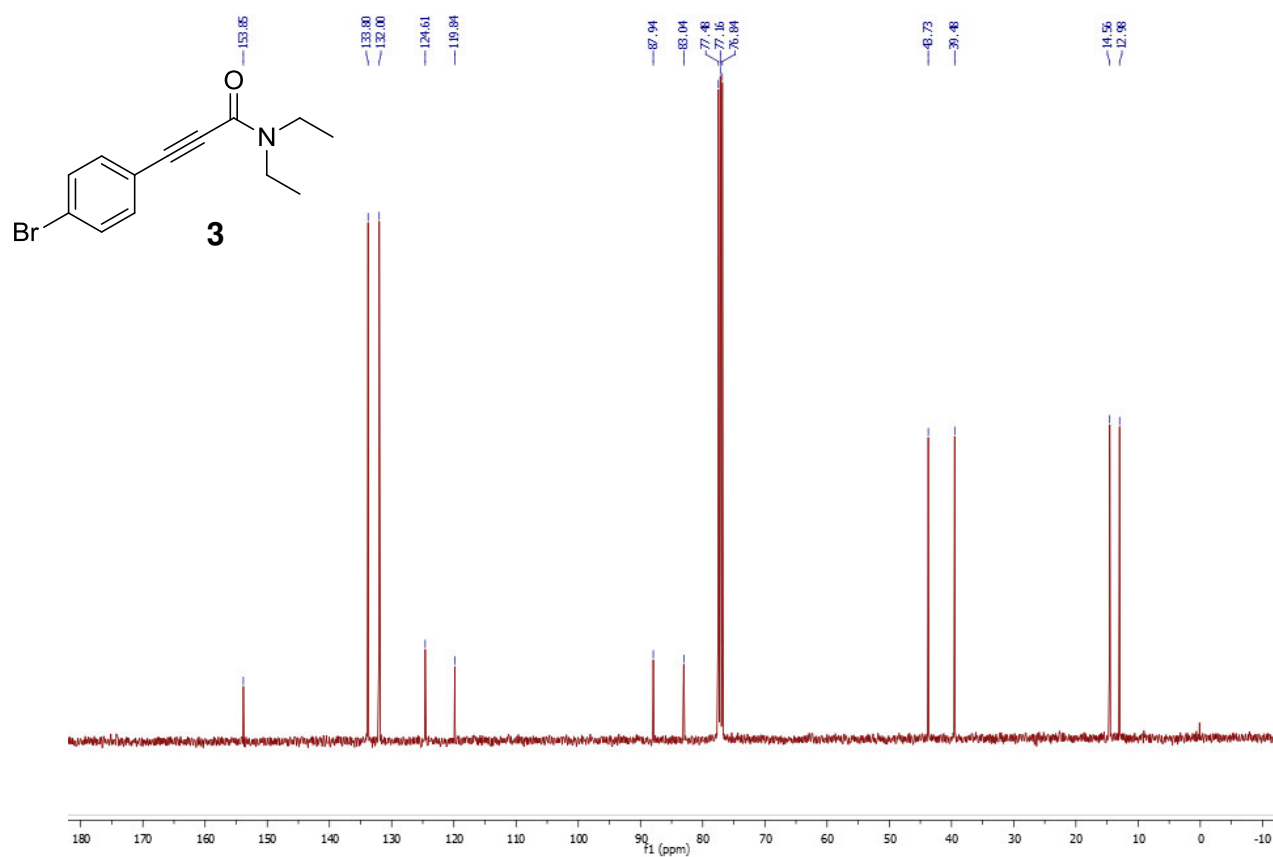
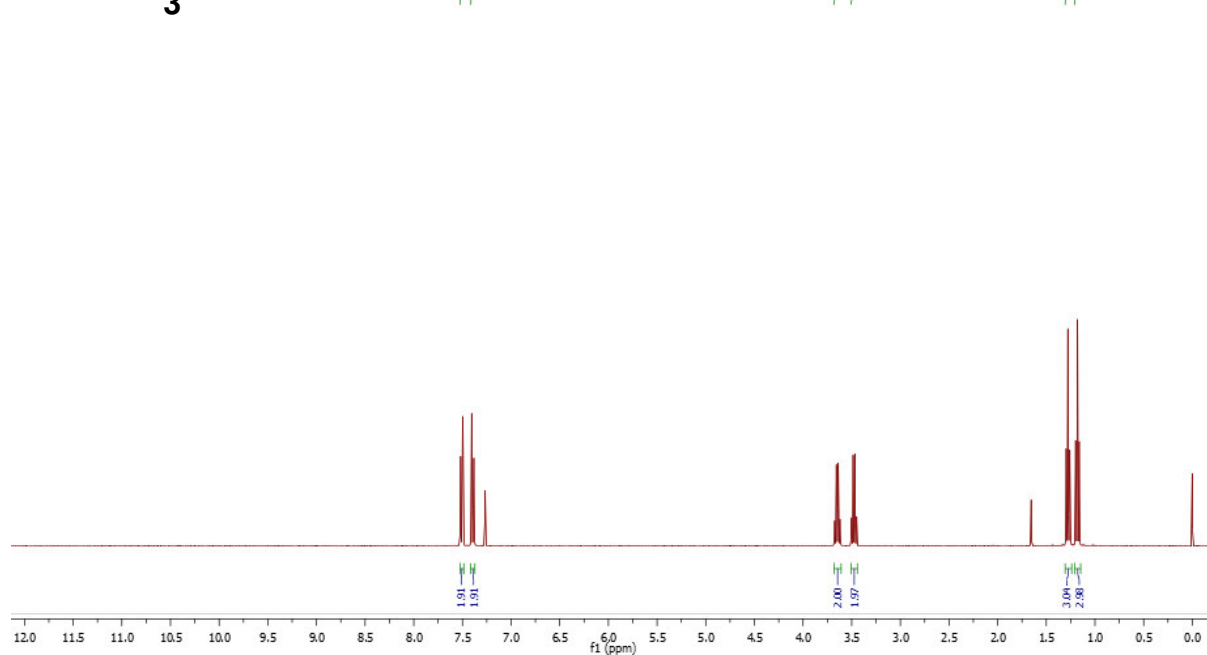
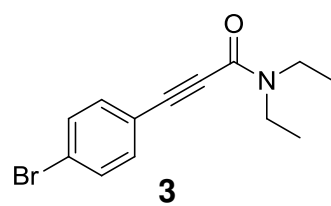


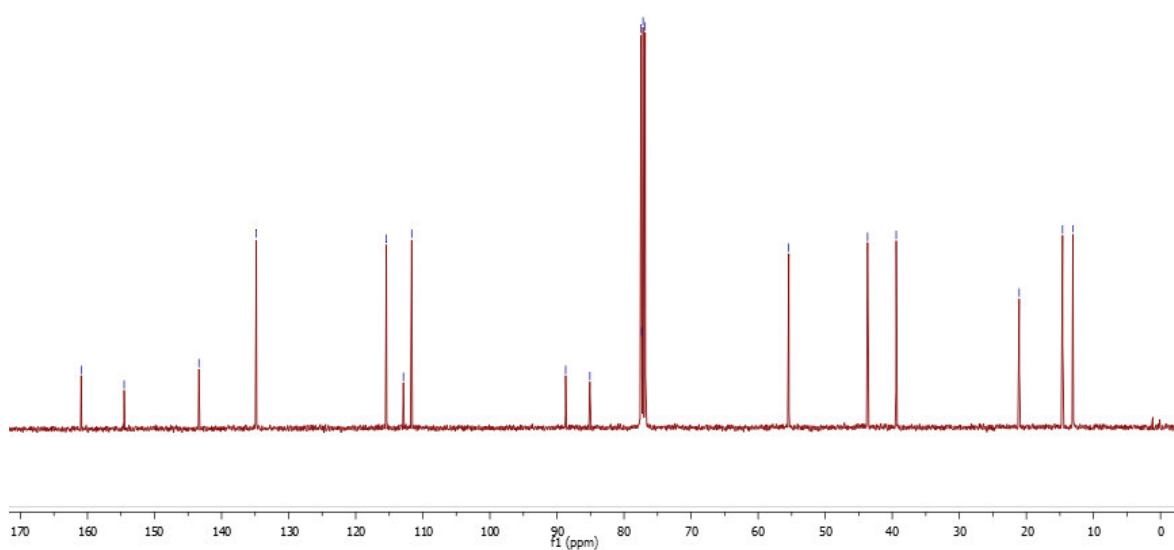
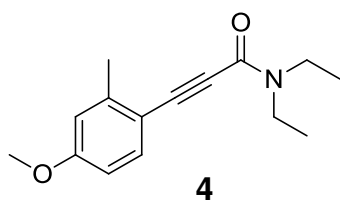
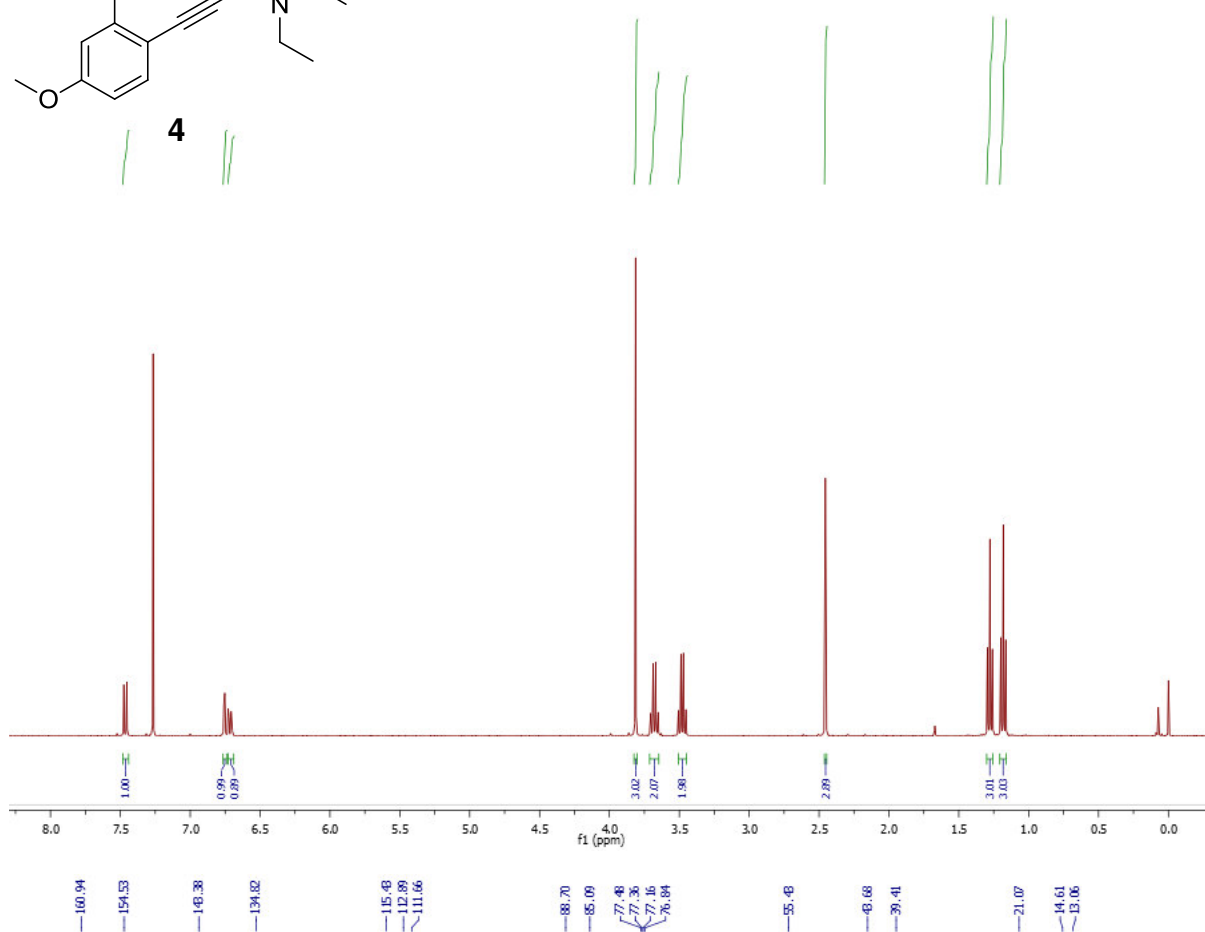
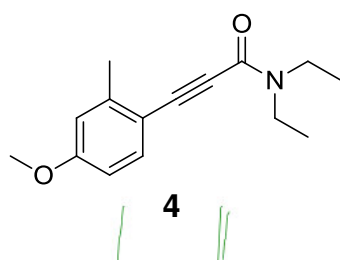
A solution of phenylacetylene (0.02 moles, 2.047 g) was treated at room temperature with N-iodosuccinimide (0.024 moles, 5.400 g) and silver nitrate (0.002 moles, 0.340 g). The reaction was stirred at room temperature for 5 hours. After this time, the reaction was filtered through a short pad of silica with hexane to give a pale yellow filtrate. This was concentrated under reduced pressure to yield an orange solid. The product was purified by silica gel flash column chromatography using an eluent of 5% EtOAc / Pet Ether to give an orange oil, (3.54 g, 77% yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.46- 7.38 (m, 2H), 7.34-7.25 (m, 3H). NMR was in accordance with literature data.⁵²

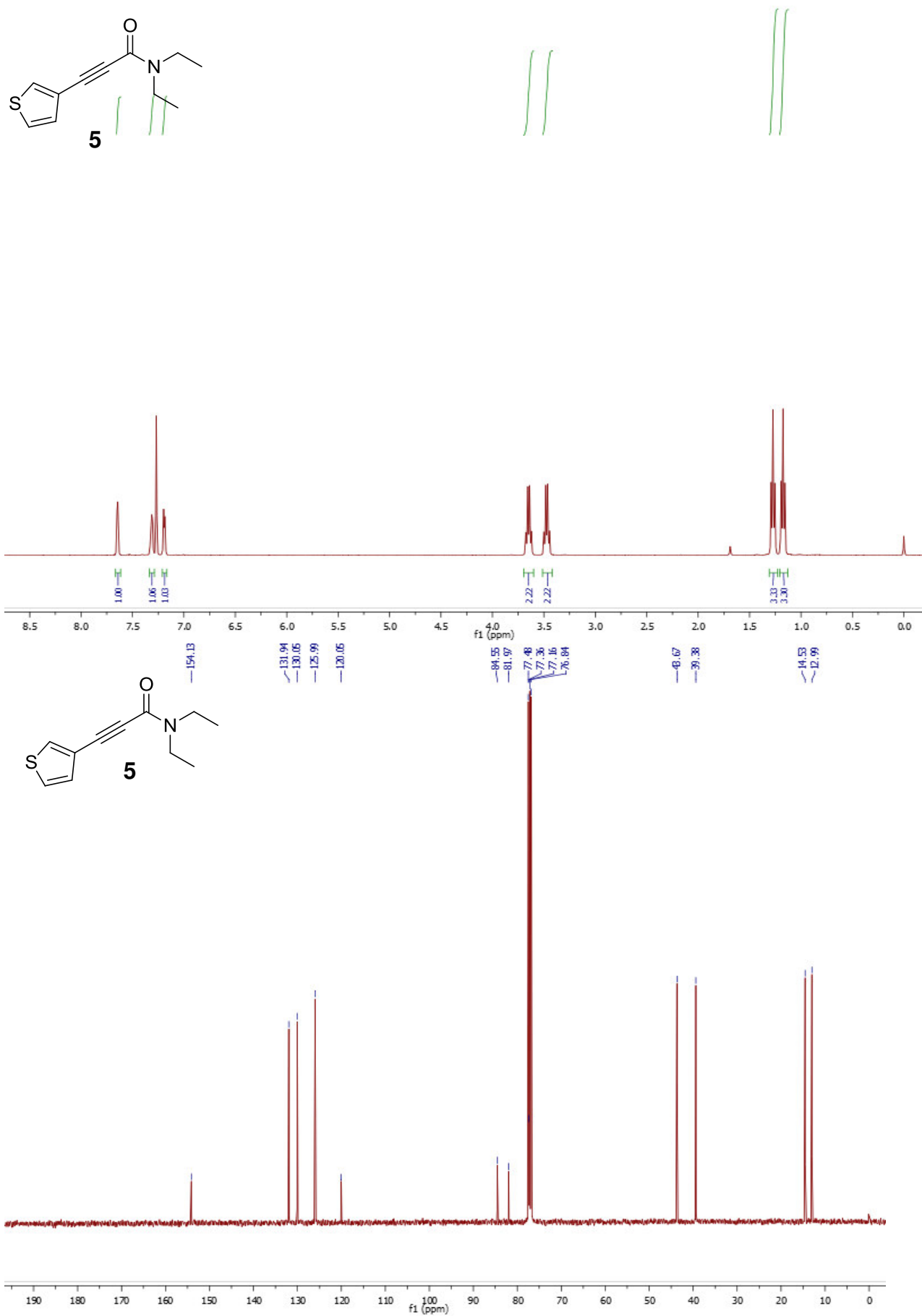
4.5.6 NMR Spectra

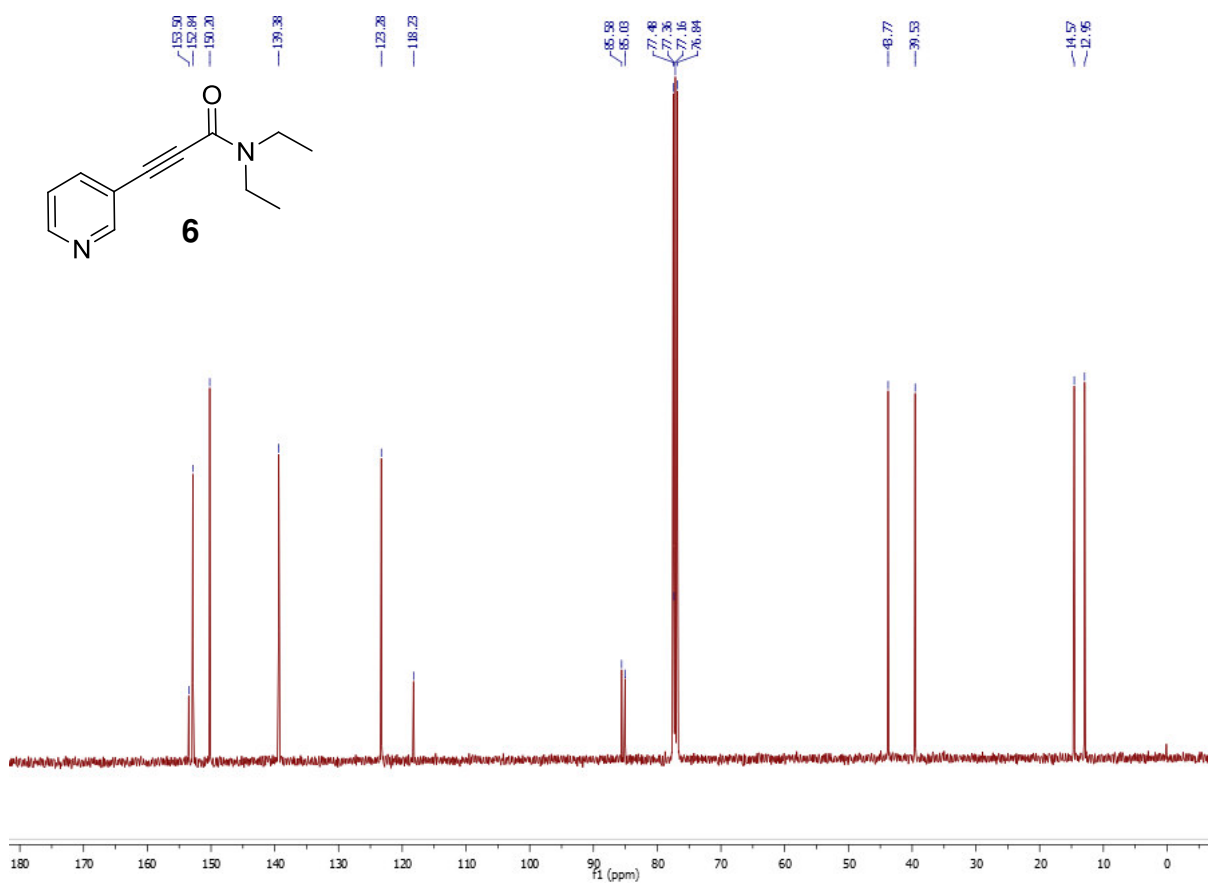
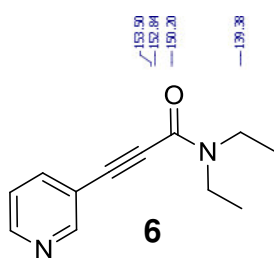
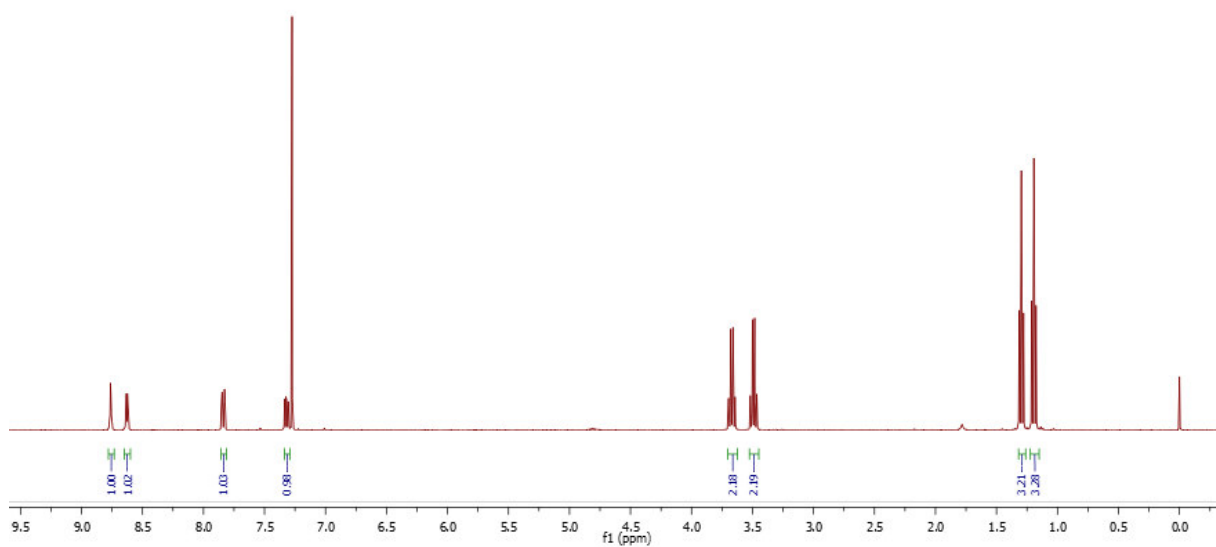
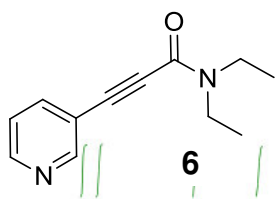


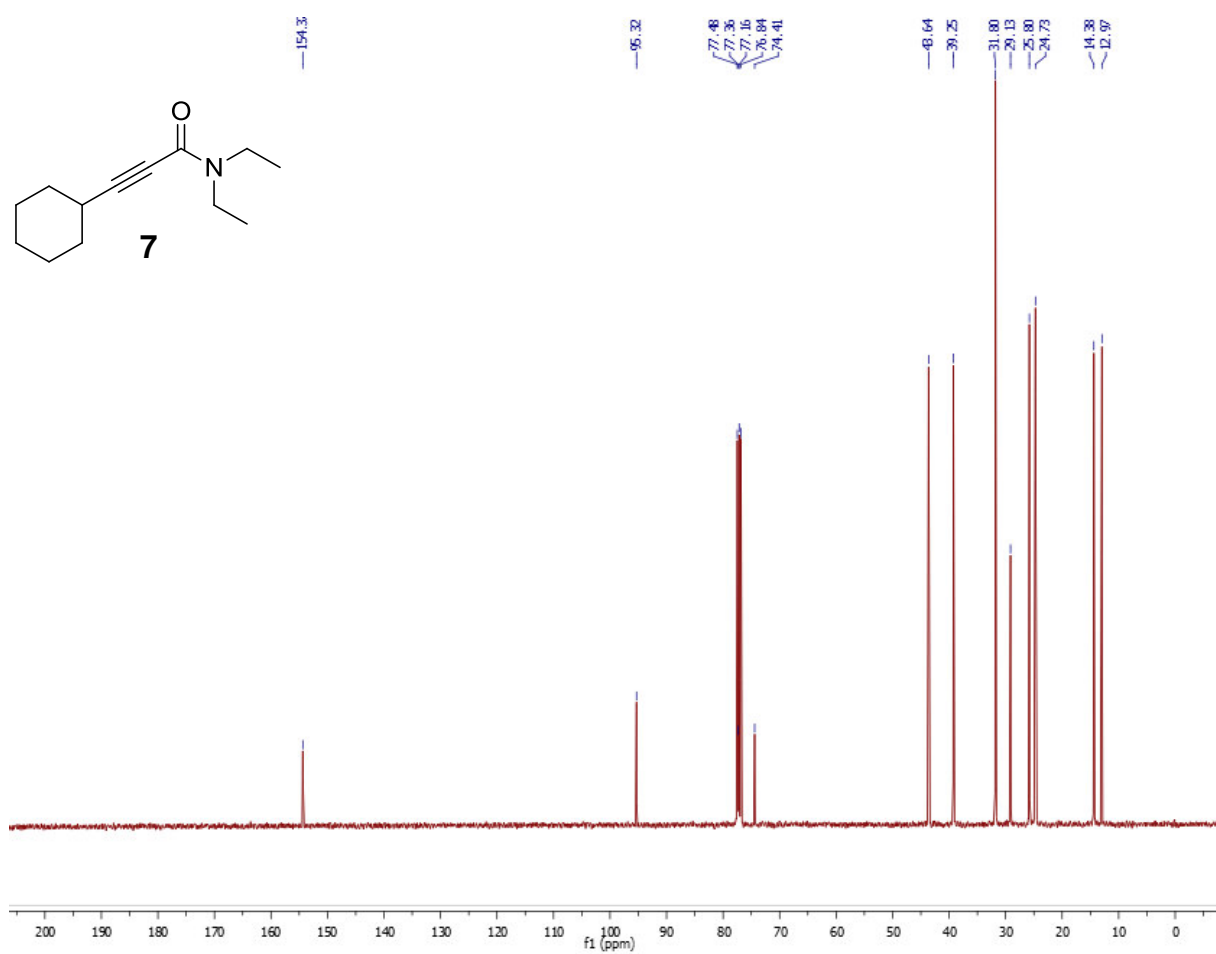
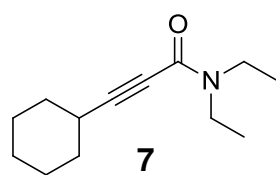
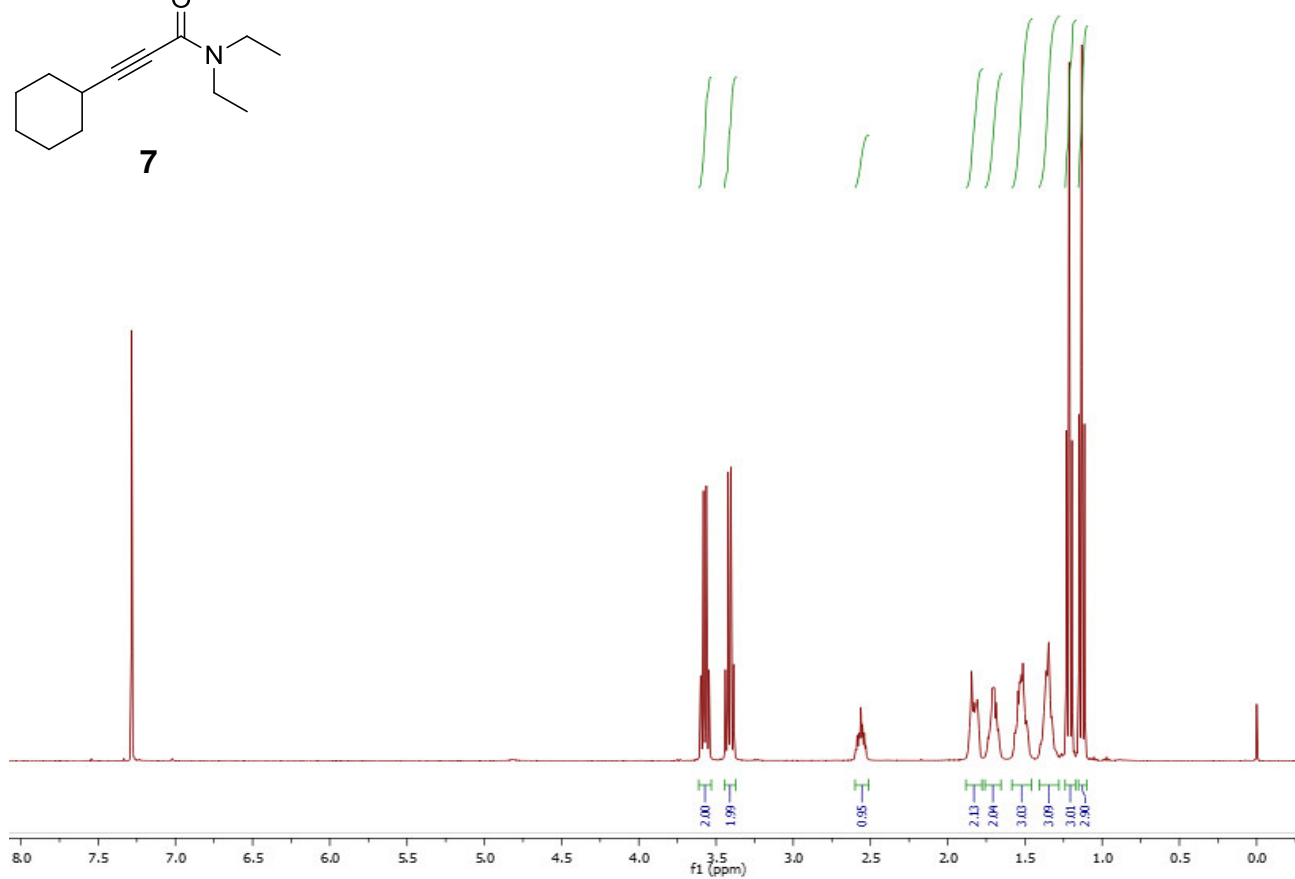
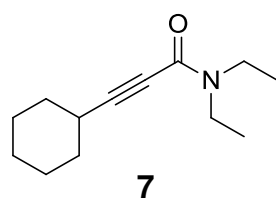


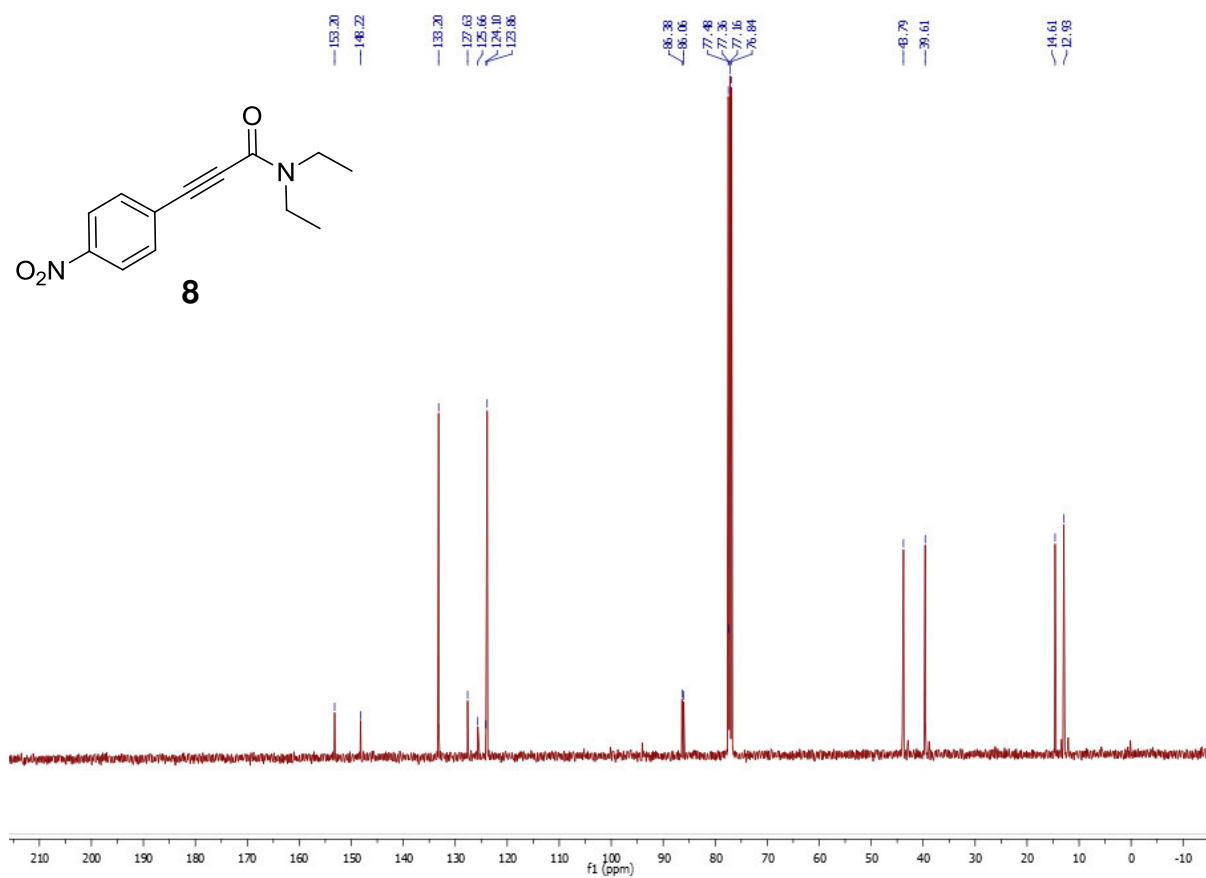
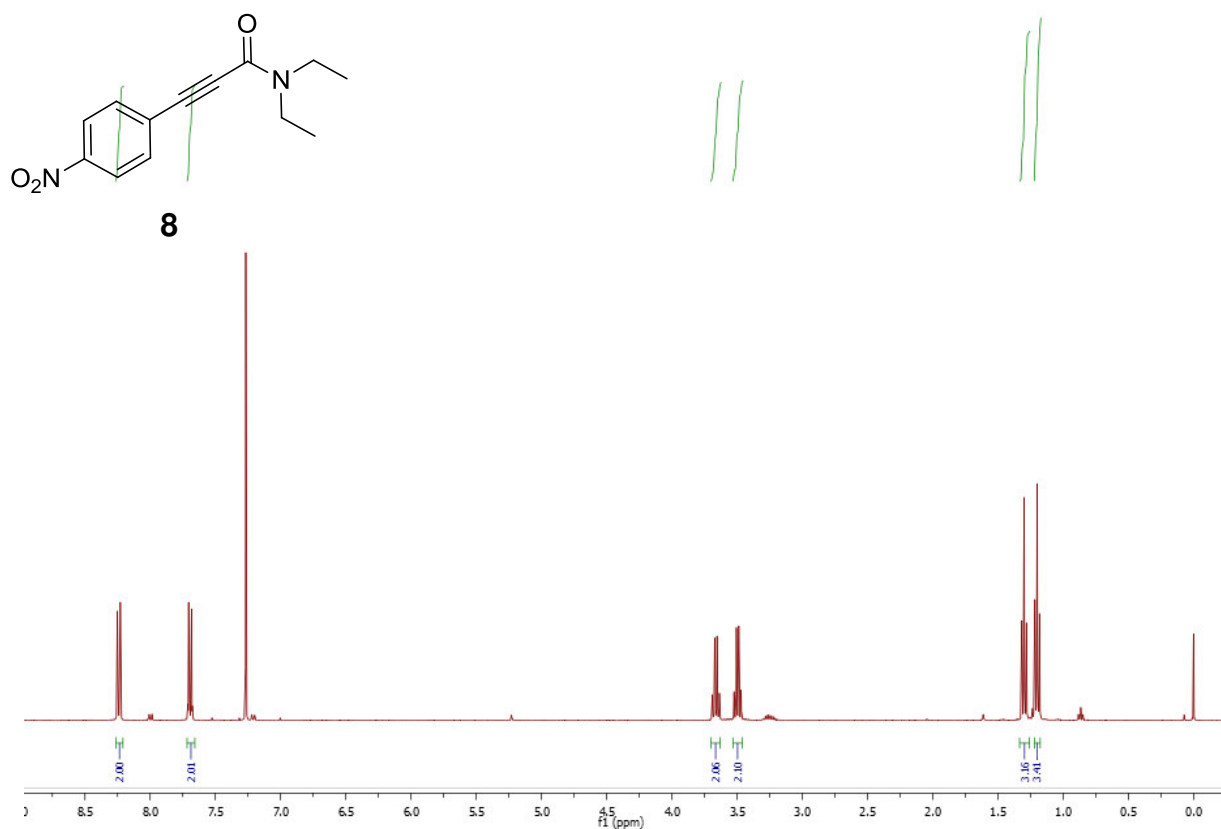


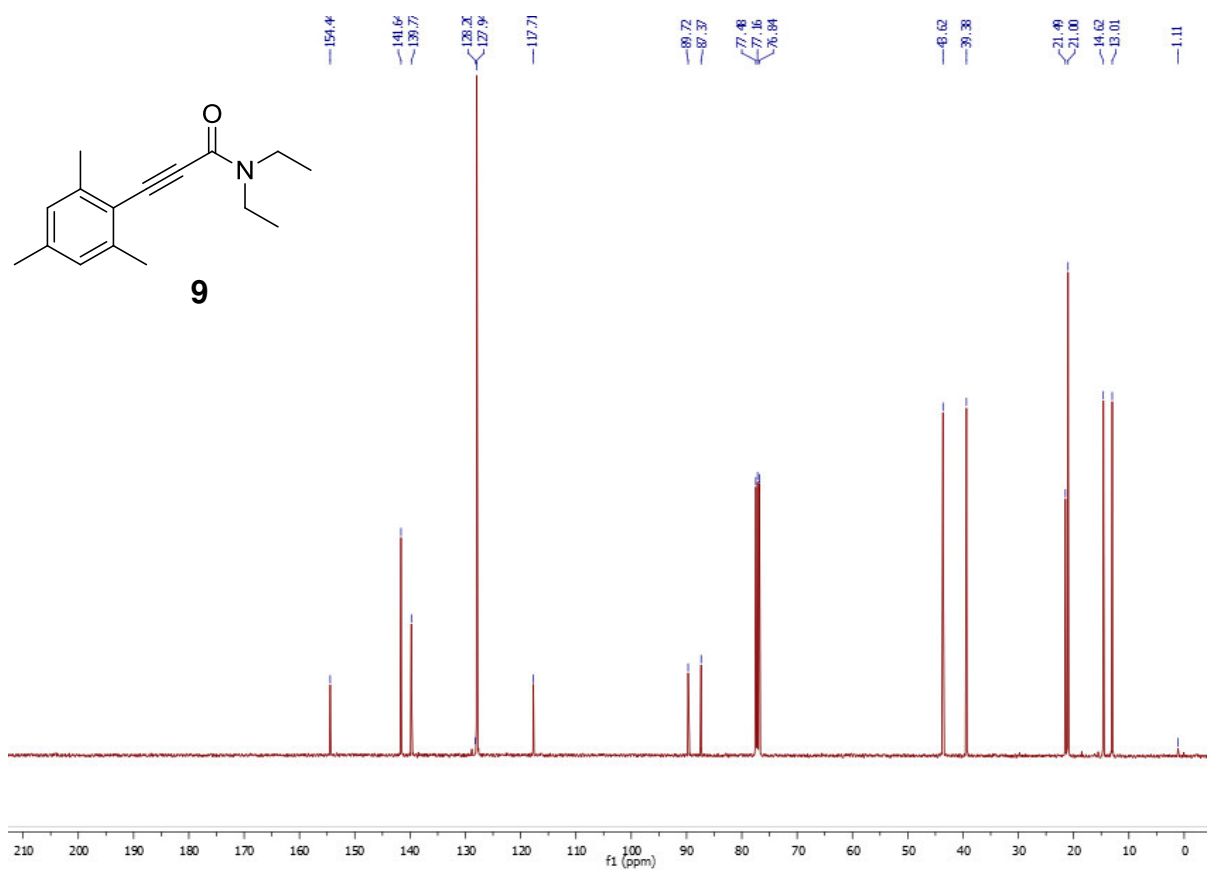
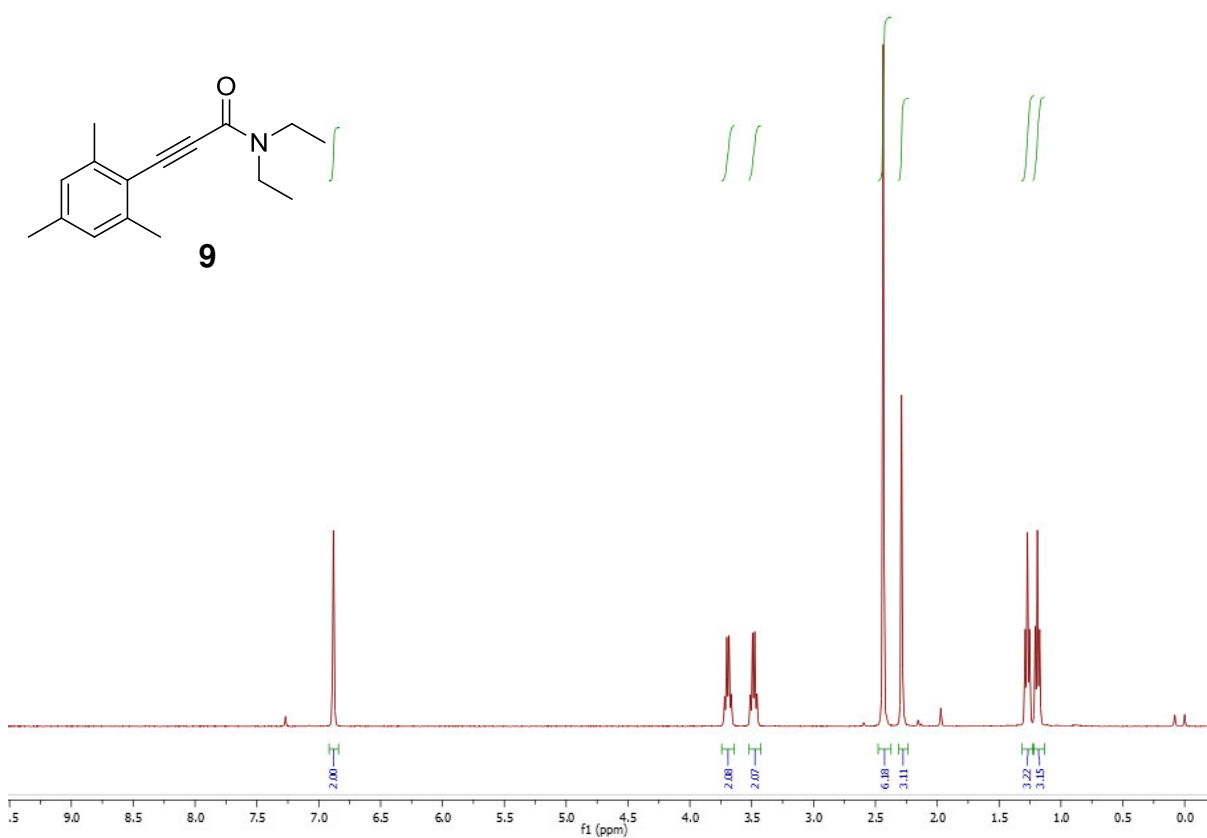


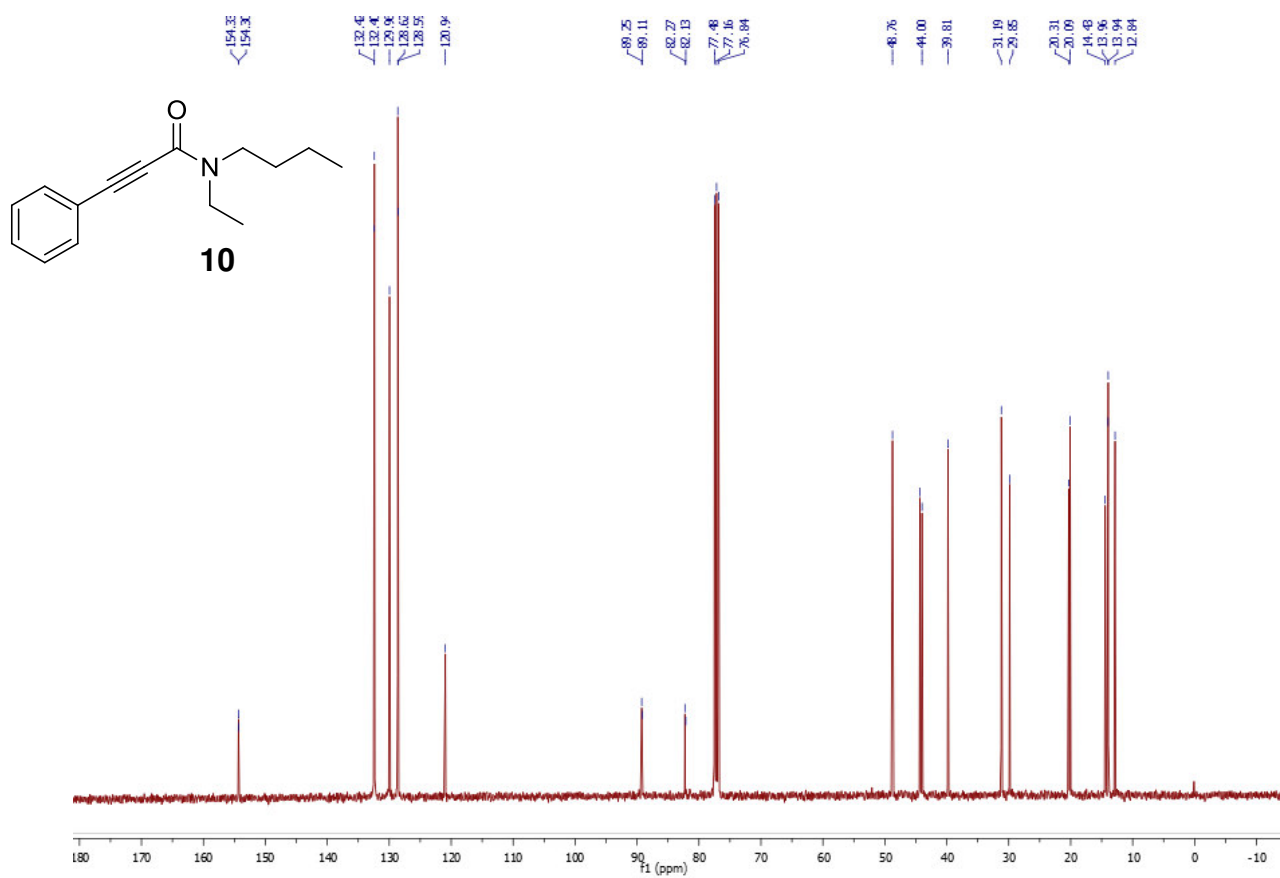
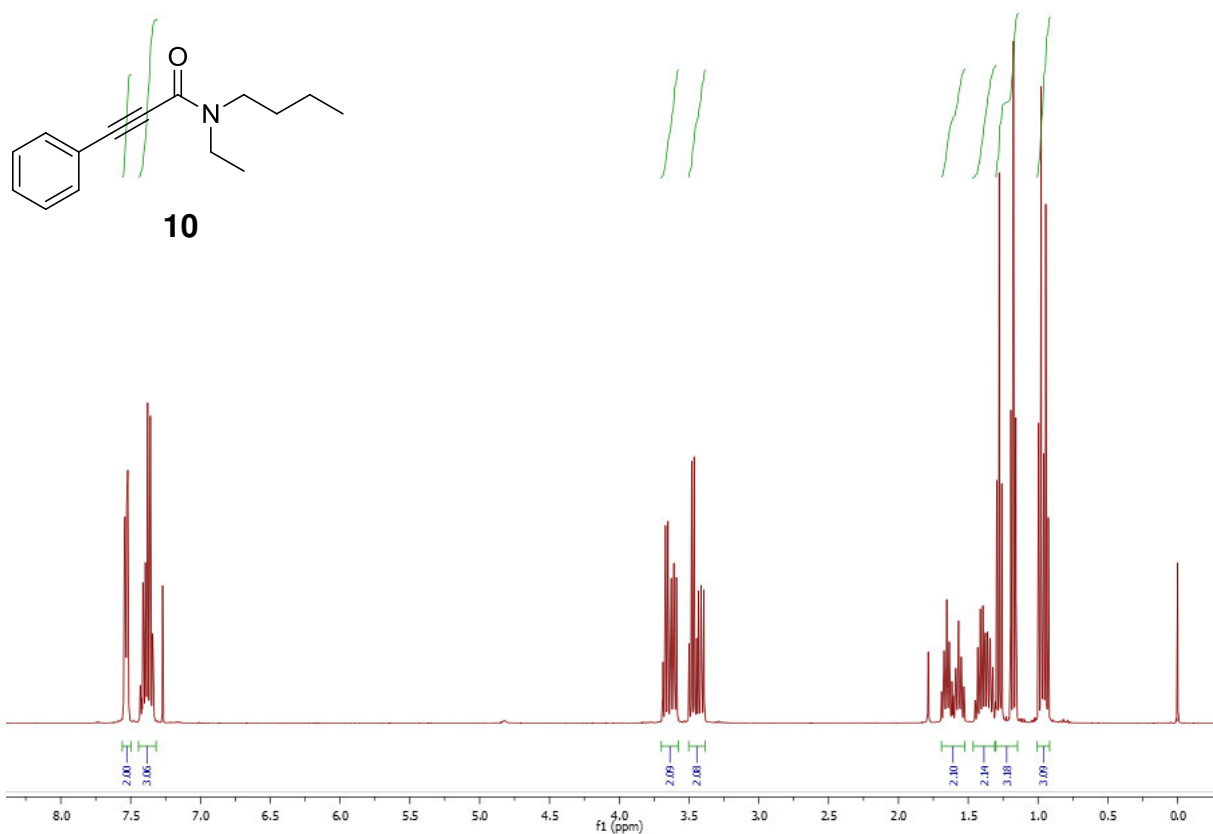


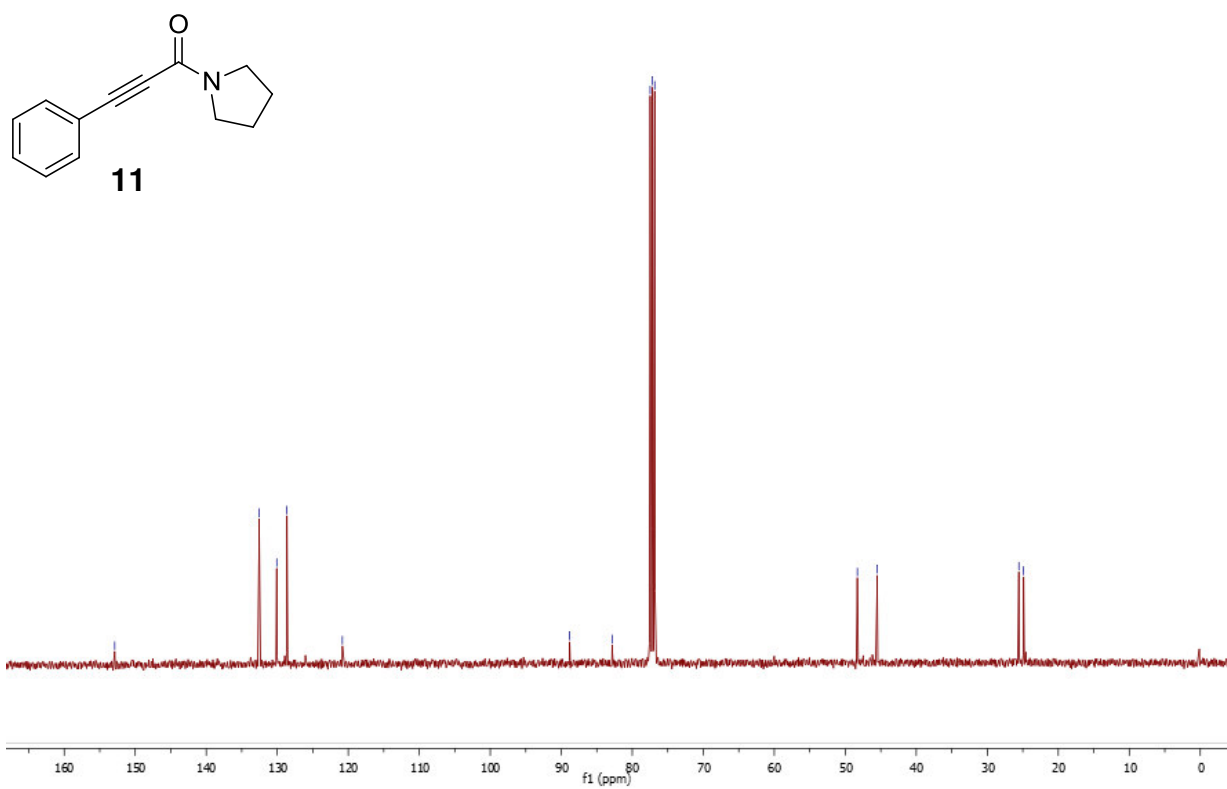
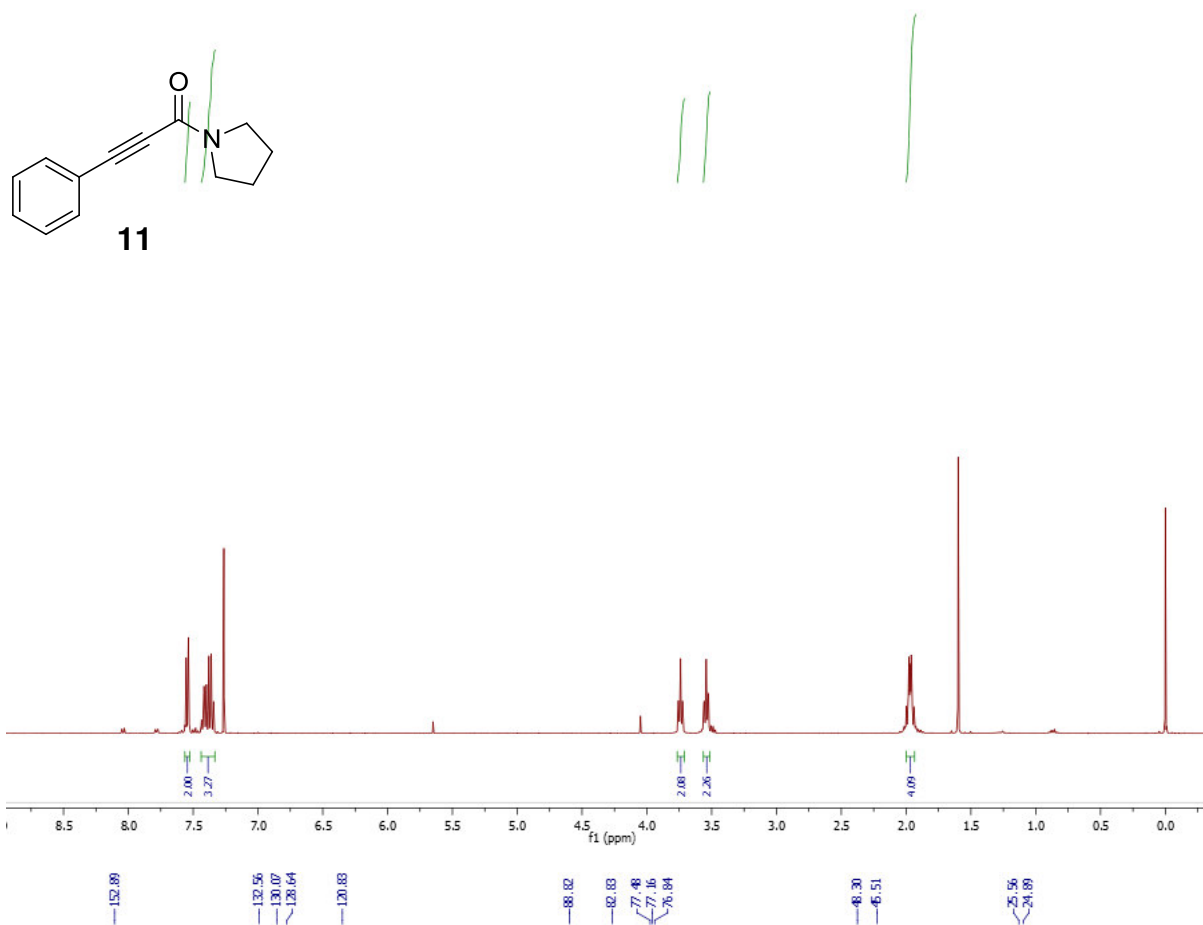


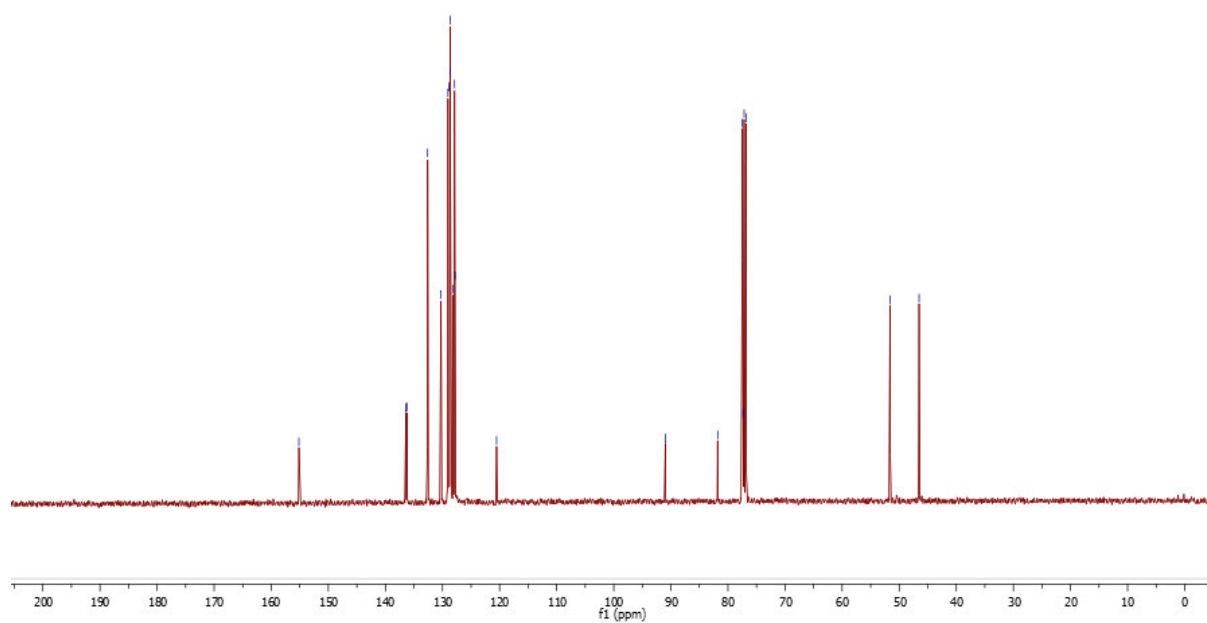
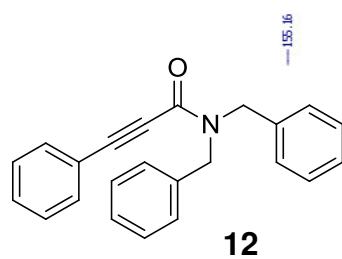
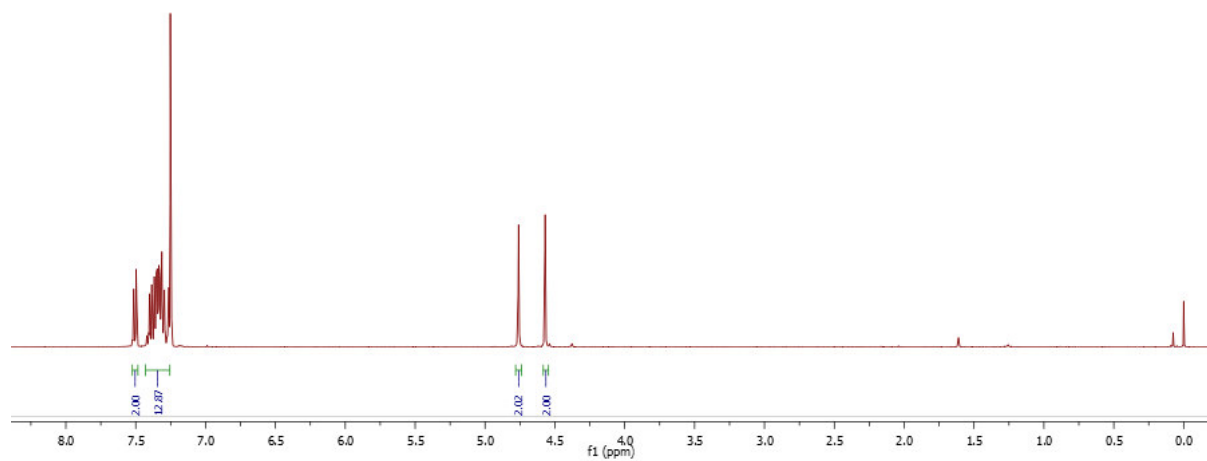
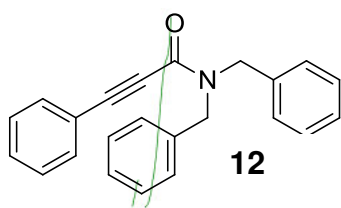


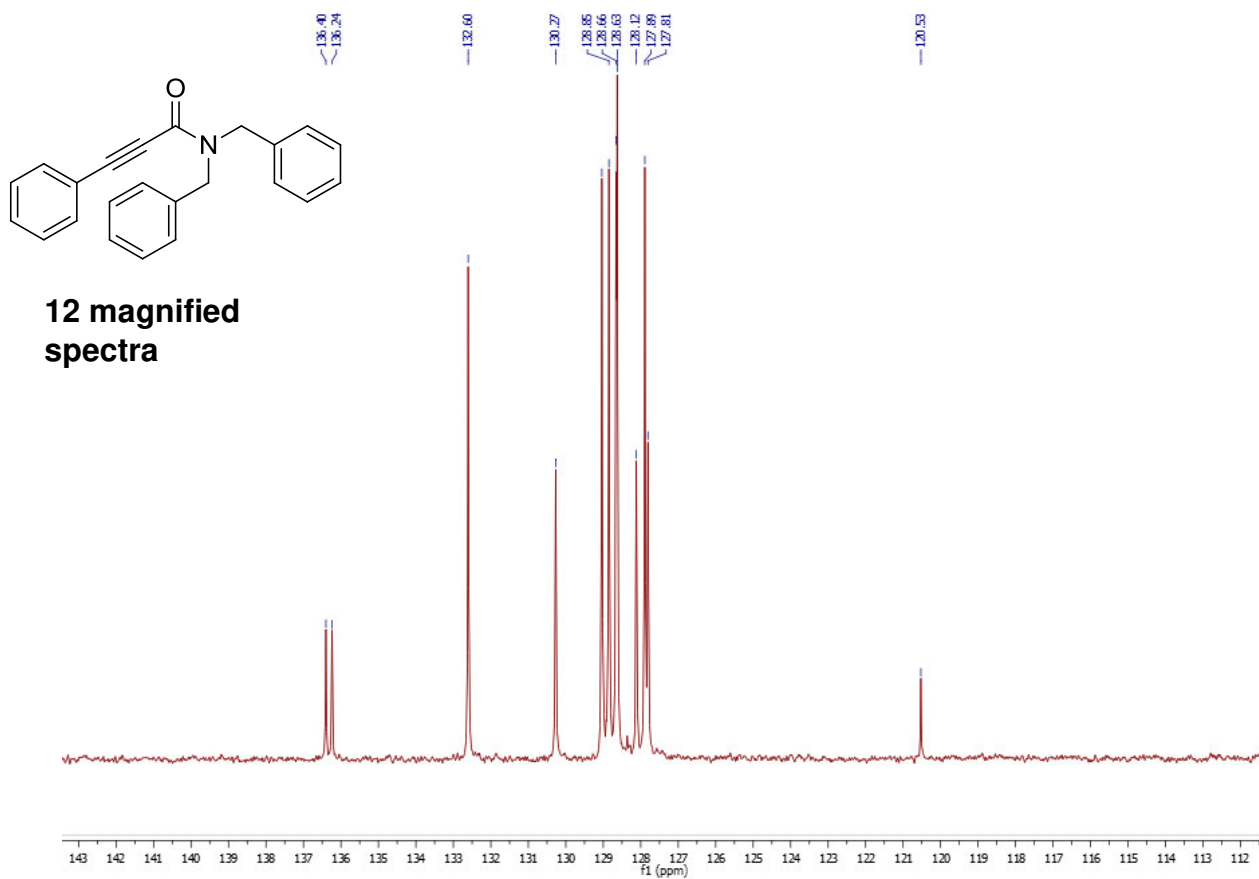


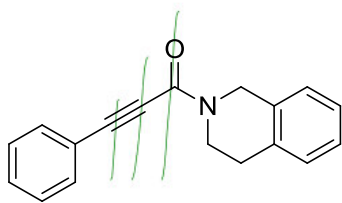




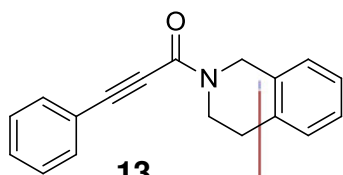
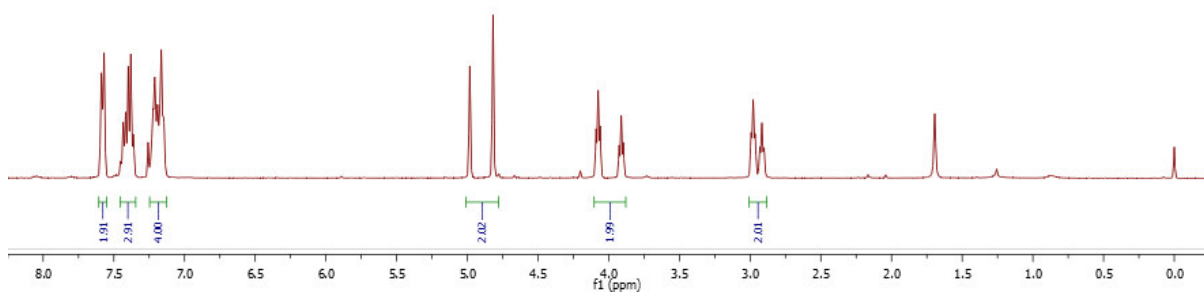




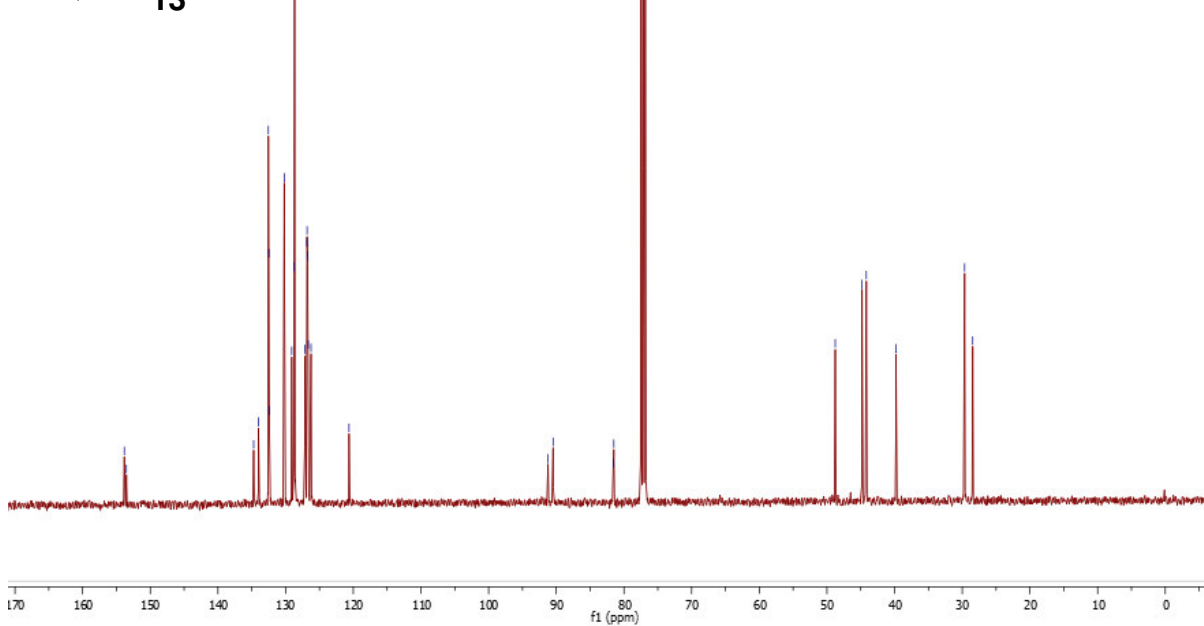


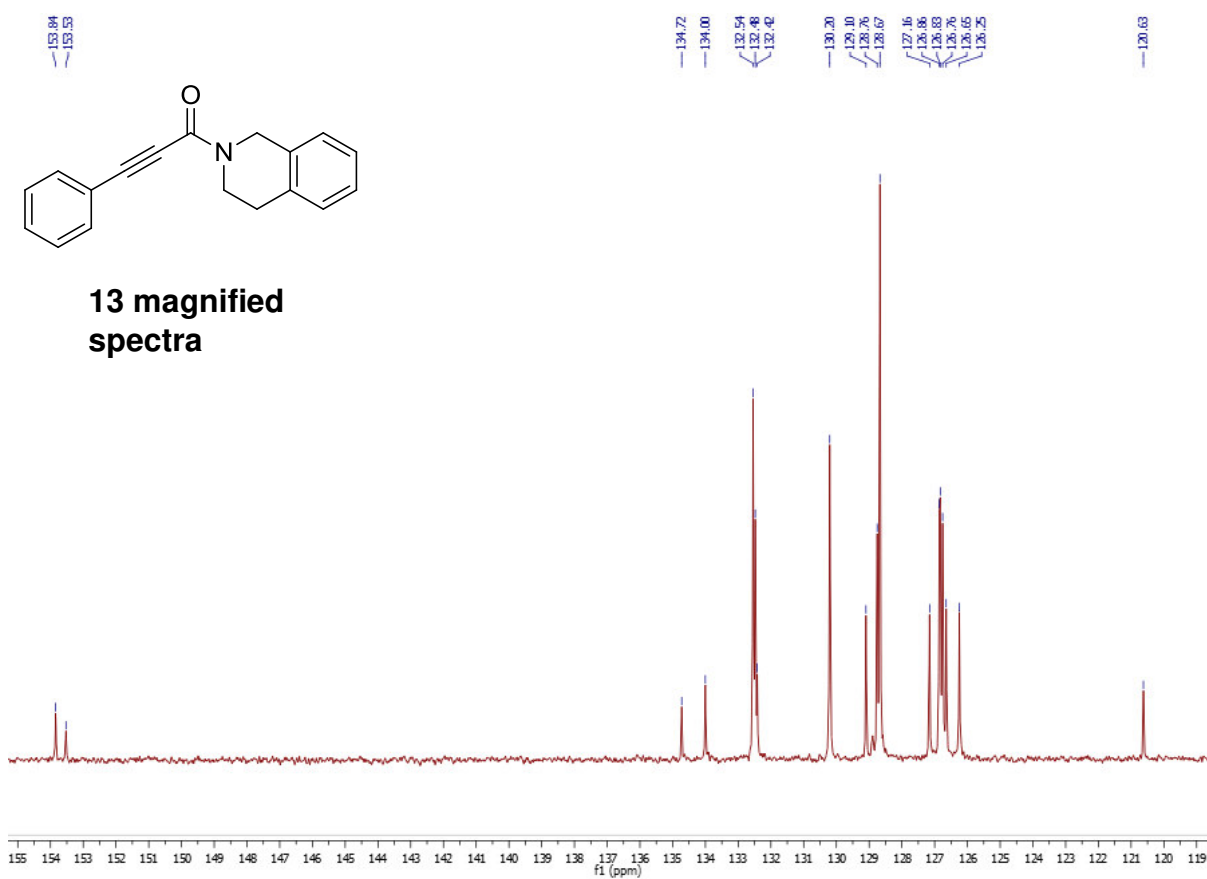


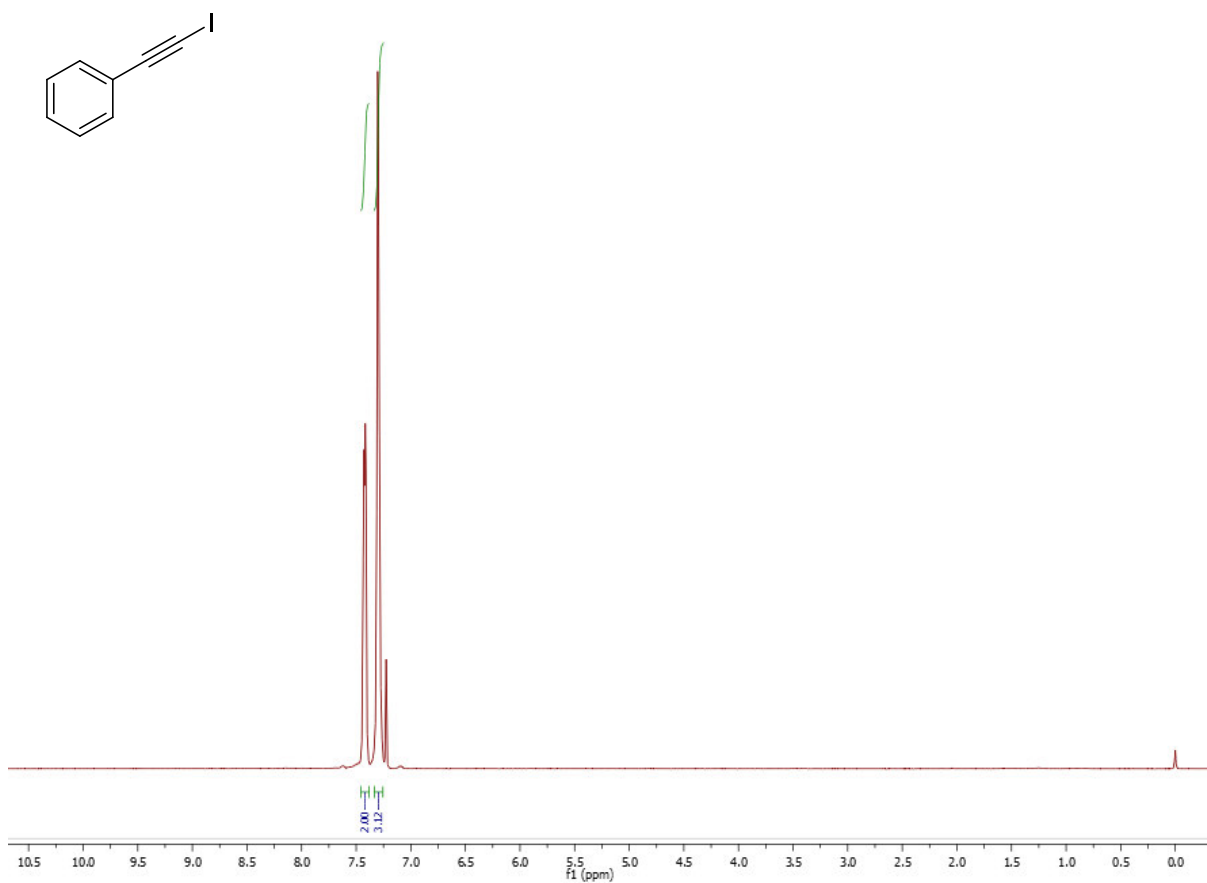
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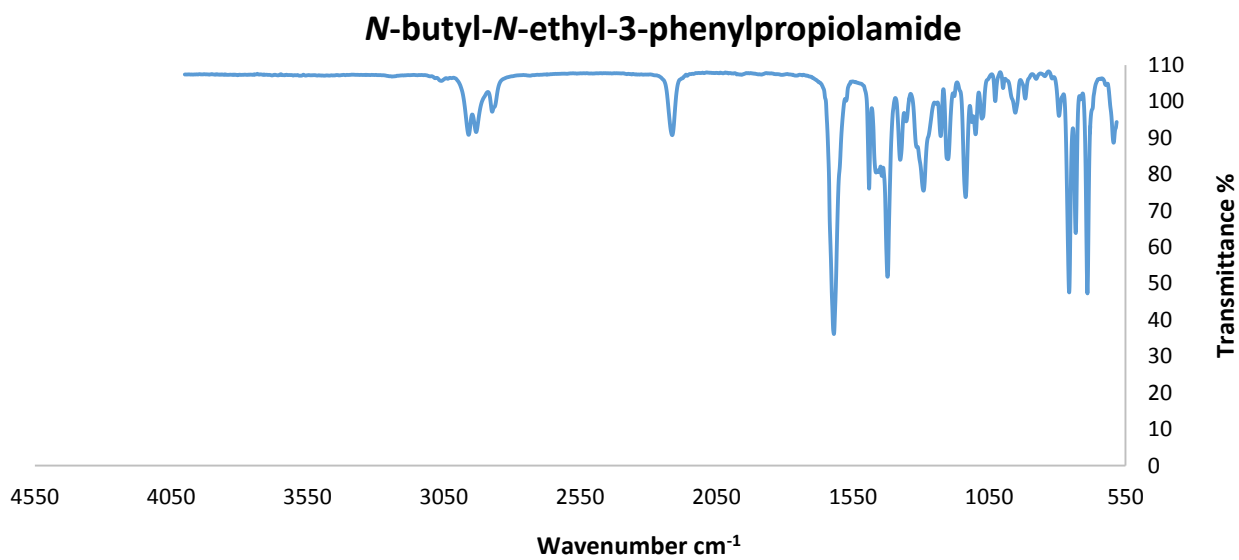
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4.5.7 Example of IR Spectra



4.6 References

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Conclusions and Future Work

In conclusion, three separate systems have been developed for the preparation of ketones, 2-alkynoates and 2-ynamides respectively. Firstly, a metal-free system was developed, that utilised nitric acid as a source of NO_x in combination with sterically unhindered nitroxyl radicals. Through this, it was possible to oxidise sterically hindered alcohols such as menthol that are commonly renowned as problematic within the literature. In addition, recycling of the radical was shown possible through the use of covalent tethering. This opens up the possibility of using nitroxyl radicals for the preparation of fine chemicals.

With regards to the synthesis of 2-alkynoates, it was shown that through the use of a TMEDA ligand, it was possible to reduce the palladium catalyst loading by over half of what had been previously reported. In addition, the use of $[\text{NBu}_4][\text{I}]$ additive resulted in a high selectivity. The substrate scope of the reaction was also improved, showing it possible to use secondary alcohols as well as a wide variety of alkynes.

Finally, it was demonstrated that the synthesis of 2-ynamides could be performed under greener, safer conditions than previously. It was possible to employ a recommended solvent, ethyl acetate, in replacement of dangerous ethereal solvents such as 1,4-dioxane. In addition, the reaction could be run under gas mixtures operating within the recommended LOC and UFL limits. The system was shown to be applicable with a range of alkynes, and both symmetric and asymmetric amines.

These results demonstrate that there is great potential for the application of catalytic aerobic oxidations in the synthesis of not only bulk chemicals, but also fine chemicals and perhaps even pharmaceuticals. In order to improve further on the work studied here, it would be beneficial to perform mechanistic studies to improve understanding of the catalytic cycle, as this would further enhance the design of second generation catalysts.

Appendix

Selected Publications

Copper(I)/ketoABNO catalysed aerobic alcohol
oxidation†

Cite this: *Catal. Sci. Technol.*, 2014, 4, 1720

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DOI: 10.1039/c4cy00219a

www.rsc.org/catalysis

Luke Rogan, N. Louise Hughes, Qun Cao, Laura M. Dornan and Mark J. Muldoon*

A Cu(I)/9-azabicyclo[3.3.1]nonan-3-one *N*-oxyl (ketoABNO) aerobic catalyst system is highly effective for the oxidation of secondary alcohols, including unactivated aliphatic substrates. The effects of pressure and gas composition on catalyst performance are examined. The radical can be employed at low loadings and is also amenable to immobilisation on to solid supports.

The selective oxidation of alcohols is an important reaction in organic chemistry. This fundamental reaction still poses problems when carried out on a larger scale, as traditional methods often use toxic reagents and/or inefficient methods.¹ There has therefore been considerable interest in developing catalytic methods for alcohol oxidation,² and in our opinion one of the best aerobic catalytic systems available is the Cu/2,2,6,6-tetramethylpiperidinyloxy (TEMPO) system.^{3,4} The most active version of this catalyst system is composed of a Cu(I) salt combined with 2,2'-bipyridine (bpy) as a ligand, *N*-methylimidazole (NMI) as a base and the stable radical TEMPO.^{4a} This system has a number of attractive features. It can oxidise a variety of alcohols including those possessing alkenes, alkynes and heteroatoms that cause significant problems for noble metal catalyst systems.^{4a} The method is also very accessible to researchers, as all catalytic components are commercially available and on a small scale it is possible to employ an "open flask" approach, using ambient air as the oxidant. One of the notable attributes of this system is the very high selectivity for primary alcohols over secondary alcohols.⁴ However, this selectivity means the catalyst is not suitable for the oxidation of secondary alcohols to ketones, a synthetically useful transformation. The poor performance of Cu/TEMPO systems for secondary alcohols is attributed to steric hindrance. The mechanism for alcohol oxidation involves the Cu complex

and radical working in unison.^{4,5} In order to efficiently oxidise secondary alcohols, replacing TEMPO with a radical that is less sterically hindered should remove this limitation. Fig. 1 shows the structures of TEMPO and some sterically unhindered stable nitroxyl radicals. Such unhindered radicals have been known since the 1960s and in fact ketoABNO was the first in this class to be reported.⁶

To date TEMPO has undoubtedly been the most widely studied stable radical used in a number of alcohol oxidation systems,³ for example, TEMPO/sodium hypochlorite type oxidations have been applied on an industrial scale.⁷ Although it was shown some time ago that such unhindered radicals are more reactive than TEMPO,⁸ it is only recently that they have been explored in oxidation catalysis. Early studies used electrochemical or chemical (primarily sodium hypochlorite) oxidants to generate the oxoammonium salt, which in turn acts as the catalyst.⁹ There have also been reports of these systems being used with O₂ as the terminal oxidant, with initial reports using NO_x type co-catalysts (*e.g.* sodium nitrite or nitric acid).¹⁰ More recently, Cu/ketoABNO and Cu/ABNO aerobic systems have been used for the oxidation of amines to imines¹¹ (and subsequent derivitisation) and the oxidation of amines to nitriles.¹²

Given the fundamental importance of alcohol oxidation we investigated the use of ketoABNO as a replacement for TEMPO. The synthesis of most unhindered radicals involves lengthy synthetic procedures and in some cases undesirable steps.¹³ ABNO can be prepared in three^{9e} or four^{10c} steps (depending on the route) and ketoABNO can be prepared in three steps.¹¹

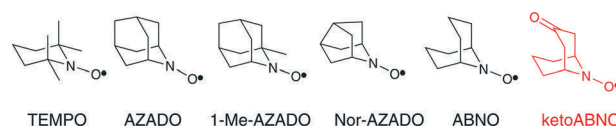


Fig. 1 Comparison of TEMPO with unhindered nitroxyl radicals.

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† Electronic supplementary information (ESI) available: Further details of experimental procedures. See DOI: 10.1039/c4cy00219a

In this initial study we have focused on three model substrates to test the ability of Cu/ketoABNO to oxidise secondary alcohols that Cu/TEMPO struggles to or indeed cannot oxidise (Fig. 2). It is known from previous studies that Cu/TEMPO systems have excellent substrate scope tolerance (e.g. heteroatom and olefin containing molecules), so we wanted to focus on this limitation of secondary alcohols and examine the reactivity for such substrates.

The substrate 1-phenylethanol was included as an example of an activated secondary alcohol that the Cu(I)/TEMPO system can oxidise.^{4a,14} The other model substrates are more challenging; 2-octanol is an aliphatic, unactivated alcohol and isoborneol is a sterically hindered, unactivated alcohol. In previous studies isoborneol has been shown as an excellent test of steric hindrance using nitroxyl radicals under hypochlorite conditions.^{9d}

In Fig. 3 we show a comparison in reactivity of ketoABNO, TEMPO and 4-oxoTEMPO for the three model substrates. Although TEMPO is commonly used, we have included 4-oxoTEMPO as perhaps this is more analogous to ketoABNO. In these reactions we used 7.5 mol% CuI, bpy and 10.5 mol% NMI with 1 mol% of the radical. In the case of TEMPO systems, typically the copper complex and radical are used at 5 mol% loadings.⁴ We had anticipated that ketoABNO would be more reactive than TEMPO, allowing the use of lower catalyst loadings. However, when the copper complex and base were reduced to 1 and 1.4 mol% respectively, performance was poor (see ESI†). When the copper complex and base were

kept at higher loadings excellent catalyst performance was observed with lower radical loadings. These results are in-line with previous mechanistic studies of Cu/TEMPO systems.^{4b,5} The radical is significantly more expensive than the copper complex, therefore, from an economical and indeed a green point of view, emphasis should perhaps be on the optimal use of the radical.

In Fig. 3 it can be seen that there is a dramatic difference in performance of ketoABNO compared to TEMPO and 4-oxoTEMPO. The radicals TEMPO and 4-oxoTEMPO can only oxidise 1-phenylethanol and no oxidation products were obtained for the unactivated alcohols 2-octanol and isoborneol. As mentioned earlier, it is known that Cu(I)/TEMPO can oxidise some activated secondary alcohols^{4a,14} and nearly 40% yield of acetophenone was obtained in four hours with this system. The yield was significantly decreased when 4-oxoTEMPO was used.

While this manuscript was in preparation, Steves and Stahl reported a study which focused on the use of Cu(I)/9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO) for aerobic alcohol oxidation.¹⁵ In their initial screening, TEMPO, 4-methoxyTEMPO and 4-oxoTEMPO were compared against ABNO, ketoABNO and AZADO (2-azaadamantane *N*-oxyl). They observed similar behaviour to that shown in Fig. 3; where the sterically less hindered radicals delivered superior reactivity to TEMPO derivatives, particularly for secondary alcohols. Unhindered radicals were compared for the oxidation of cyclohexanemethanol at loadings of 5 mol% Cu complex and 5 mol% radical. It was found that all of the aforementioned unhindered radicals delivered similar reactivity under these conditions. Their study primarily focused on the use of ABNO and the catalyst system was further optimised to: 5 mol% Cu(MeCN)₄OTf, 5 mol% 4,4'-dimethoxy-2,2'-bipyridine (MeO**bpy**), 10 mol% NMI and 1 mol% ABNO. This system was used to oxidise a wide range of primary and secondary alcohols at room temperature and at these loadings, most substrates were fully converted in 1 h. This catalyst system was tolerant of a range of functionalities (e.g. heteroatoms, alkenes and alkynes) similar to that previously observed for Cu(I)/TEMPO.^{4a} Substrates that could bind tightly or chelate with the Cu catalyst were found to be unreactive, again similar to that observed for Cu(I)/TEMPO.^{4a}

In our studies we have not focused on a wide range of substrates. Rather, we wished to further examine the reactivity of our Cu(I)/ketoABNO system for the three representative substrates shown in Fig. 2, as well as the development of a solid supported ABNO derivative.

In Fig. 3 it can be seen that under these reaction conditions ketoABNO enabled the oxidation of all three secondary alcohols at a very similar rate. This is unusual, as normally activated alcohols react much faster than aliphatic alcohols. This is arguably the case for all catalysts,² including Cu/TEMPO,⁴ although aerobic Cu/TEMPO studies have been limited to primary alcohols. Given that the reactions shown in Fig. 3 are carried out in "open flask" it was possible that, under these conditions, the reactions with ketoABNO were mass transfer limited in O₂. To test our theory we examined

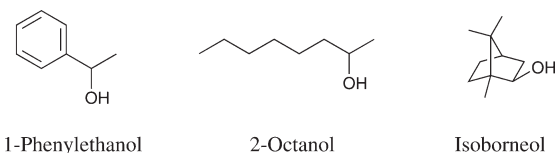


Fig. 2 Secondary alcohols used as model substrates.

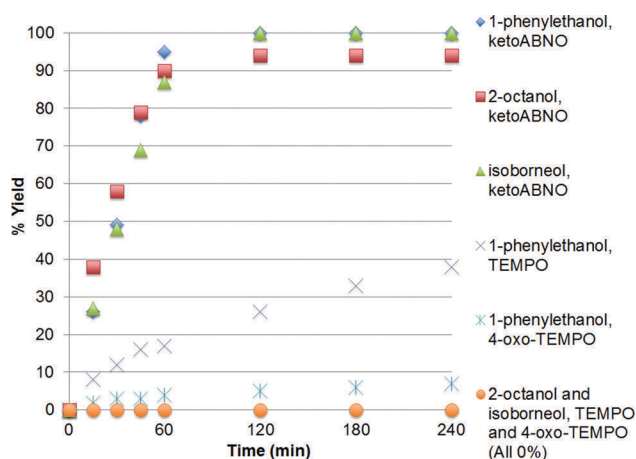


Fig. 3 Comparison of ketoABNO, TEMPO and 4-oxoTEMPO for the oxidation of secondary alcohols. Reaction conditions: 1 mmol of substrate in acetonitrile (5 mL), nitroxyl radical (1 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, ambient air, stir rate = 340 RPM.

the influence of stir rate on the reaction. We examined stirrer speed effects with 1 mol% and 0.1 mol% loadings of ketoABNO for both 1-phenylethanol and 2-octanol. Different stirrer speeds were tested using a standard round bottom flask set-up, open to the air. There is arguably a limit to how much you can improve the efficiency of the gas-to-liquid mixing using such a set-up, therefore we also employed a mechanically stirred reactor/view cell with a constant flow of air supplied to avoid O₂ depletion (see ESI† for further details). This reactor meant we had to carry out reactions on a slightly larger scale; however, it is specifically designed for efficient mixing. It has a gas entrainment stirrer, which at high operating speeds (in this case 2400 RPM) delivers excellent dispersion of gases into the liquid phase. The reactor also has a viewing window that allows observation of the mixing, and we could see that at the high stir rate the mixture was very well mixed and highly aerated.

In Fig. 4 we can see that for the reaction of 1-phenylethanol at 1 mol% ketoABNO loading the system is indeed mass transfer limited in O₂ under the conditions used in Fig. 3. With improved mixing, the rate of reaction increases, with the best performance obtained in the reactor with a gas entrainment stirrer. Consistent with these results, it is worth mentioning a relevant study by Mase *et al.*, which showed that using a “microbubble generator” to improve gas transport led to faster oxidation of activated alcohols with a Cu/TEMPO catalyst system.¹⁶

When the loading of ketoABNO is dropped to 0.1 mol%, it can be seen in Fig. 5 that there is less of an impact from stirrer speed, and it is possible to obtain similar reaction rates in both the flask and the reactor.

Fig. 6 shows the reaction course using 1 mol% ketoABNO for 2-octanol at a range of stirrer speeds and also isoborneol at the most efficient stirrer speed. Unlike that previously observed in Fig. 3, when we compare the three model substrates with efficient mixing we now see that the reaction is significantly faster for the activated substrate 1-phenylethanol

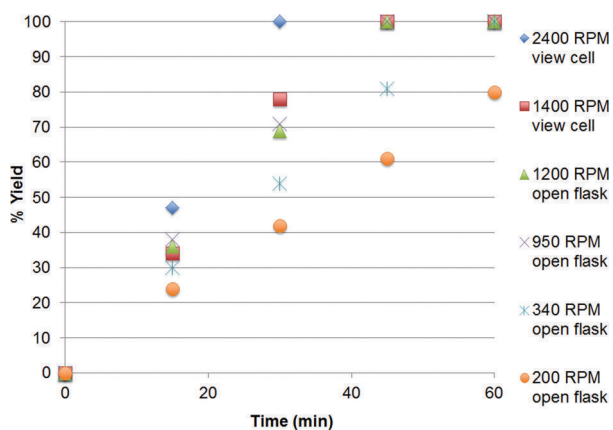


Fig. 4 Stir rate effects on the oxidation of 1-phenylethanol. Reaction conditions: ketoABNO (1 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, ambient air. “open flask” = 1 mmol substrate scale, “view cell” = 7 mmol substrate scale.

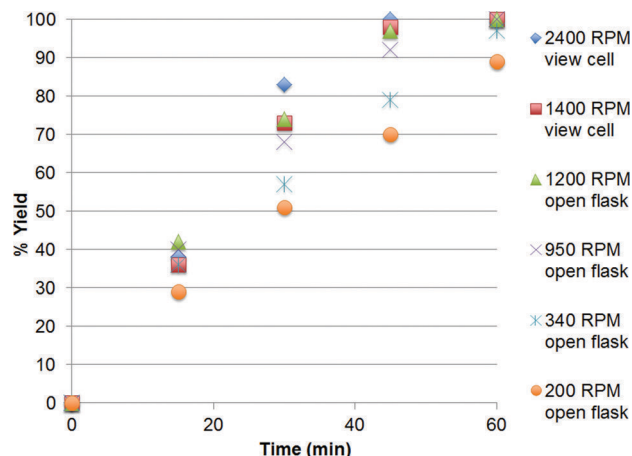


Fig. 5 Stir rate effects on the oxidation of 1-phenylethanol. Reaction conditions: ketoABNO (0.1 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, ambient air. “open flask” = 1 mmol substrate scale, “view cell” = 7 mmol substrate scale.

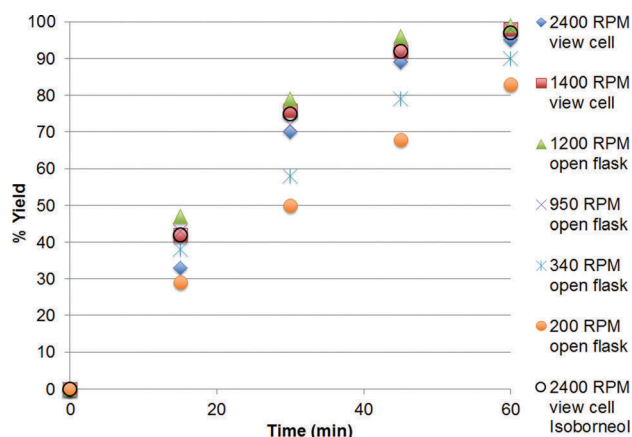


Fig. 6 Stir rate effects on the oxidation of 2-octanol and isoborneol. Reaction conditions: ketoABNO (1 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, ambient air. “open flask” = 1 mmol substrate scale, “view cell” = 7 mmol substrate scale.

(*c.f.* Fig. 4 and 6). It is clear that for these aliphatic substrates, even at 1 mol% it is possible to get out of the mass transfer limited regime using a round bottom flask.

Fig. 7 shows stirring effects for the aliphatic substrates using the lower loading of 0.1 mol% ketoABNO. This figure once again highlights the difference between aliphatic substrates and activated substrates. With the less reactive substrates and lower loading of radical it is clear that stirring has essentially no effect on the reaction rate.

We also wanted to examine the effects of pressure on these reactions. The majority of studies on such metal/nitroxyl catalysts utilise ambient air or low pressures of O₂ (*e.g.* 1 atm). Kinetic studies by Hoover and Stahl demonstrated that Cu(I)/TEMPO systems exhibited a first order dependence on O₂ pressure.⁵ In those studies they utilised a pure O₂ atmosphere and the pressure was varied over quite a narrow range (up to 900 Torr (= 1.2 bar)). In our studies we have utilised air

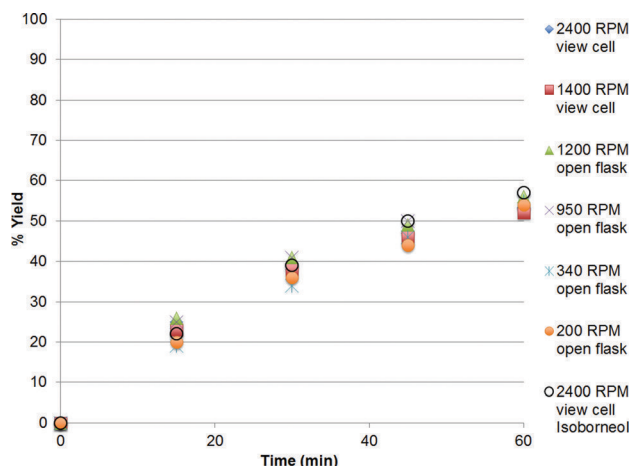


Fig. 7 Stir rate effects on the oxidation of 2-octanol and isoborneol. Reaction conditions: ketoABNO (0.1 mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, ambient air. "open flask" = 1 mmol substrate scale, "view cell" = 7 mmol substrate scale.

and 8% O₂ (in N₂) at pressures of 40 bar and compared these to "open flask" conditions. This is relevant because dilute oxygen mixtures would most likely be employed if such systems were used in industry.¹⁷ In fact a continuous flow system would probably be employed to further improve safety and scalability. Using dilute O₂ mixtures usually means higher pressures are required. For example, Stahl and co-workers have examined Cu(I)/TEMPO alcohol oxidation in a continuous flow system utilising 9% O₂ (in N₂) at a pressure of 35 bar.¹⁸ Fig. 8 shows the results from our studies examining the oxidation of 1-phenylethanol at different loadings of ketoABNO along with different pressures and O₂ compositions.

The results in Fig. 8 highlight a number of interesting features. It can be seen that applying a pressure of 40 bar of air or 8% O₂ (in N₂) enables a significant increase in rate with

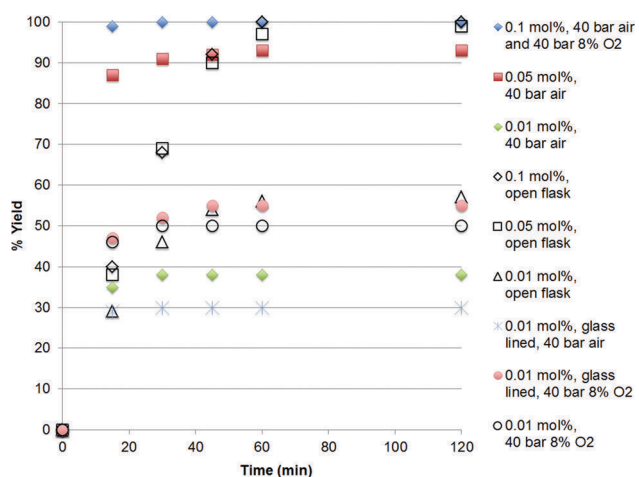


Fig. 8 Influence of gas pressure and composition on the oxidation of 1-phenylethanol. Reaction conditions: 1 mmol of substrate in acetonitrile (5 mL), ketoABNO (X mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, stir rate = 950 RPM. "open flask" = ambient air, pressurised reactions carried out in small reactors (see ESI†).

complete conversion of 1-phenylethanol in just 15 min with only 0.1 mol% of ketoABNO. Such fast reaction rates make these reactions very suitable for continuous flow conditions. Impressively we can also obtain essentially complete conversion in 1 h with just 0.05 mol% of ketoABNO. At this catalyst loading it can be seen that a very high conversion is obtained in just 15 minutes, however by 45 min the same yield can be obtained with the open flask method. These results hinted that higher O₂ pressures may lead to faster catalyst decomposition and when we lowered the loadings of ketoABNO further this does indeed seem to be the case. A loading of 0.01 mol% ketoABNO gives better performance in the open flask than under 40 bar of air pressure. It is worth pointing out that mechanistic studies on Cu(I)/TEMPO indicate that the copper co-catalyst is involved in the re-oxidation/regeneration of the radical,⁵ consequently at such low loadings of radical, the copper co-catalyst has to perform this task a greater number of times. We wondered if the stainless steel reactors were contributing to decomposition of the copper co-catalyst, as this has been observed previously.¹⁸ However, we found that the performance with 40 bar of air in a glass-lined reactor was similar to that in a stainless steel reactor. A reaction was carried out in the glass lined reactor with 8% O₂ (40 bar) and it can be seen in Fig. 8 that the performance improves. This supports the theory that higher O₂ concentrations can lead to increased catalyst decomposition. We believe that higher O₂ concentrations could be leading to decomposition of the copper co-catalyst. As mentioned earlier, to obtain good reaction rates we require high concentrations of the copper co-catalyst and poor performance is seen with loadings of just 1 mol% copper complex (see ESI†). A number of groups have previously discussed decomposition pathways for the copper co-catalyst in Cu/TEMPO systems,^{4b,5} with insoluble/unreactive copper hydroxide or oxide species proposed as possible decomposition products. Such decomposition is perhaps further accelerated at higher O₂ concentrations.

We also examined the oxidation of 2-octanol and isoborneol at lower ketoABNO loadings (0.1 and 0.01 mol%) with higher pressures of O₂ (Fig. 9). In these experiments we once again found that the oxidation of the aliphatic substrates was significantly slower than 1-phenylethanol. Additionally, a similar effect of O₂ pressure was observed, albeit earlier in the reaction and at 0.1 mol% ketoABNO the open flask was superior to high pressure air.

Although more detailed mechanistic studies are needed, the trends that we have observed for reactivity of activated *versus* unactivated substrates would suggest that the mechanism is the same as that previously determined for Cu(I)/TEMPO oxidation of primary alcohols.⁵ With Cu(I)/TEMPO Hoover and Stahl determined that for activated alcohols, oxidation of the catalyst is the turnover limiting part of the catalyst cycle, while for less reactive aliphatic substrates, both substrate oxidation and catalyst oxidation contribute to the overall rate. For the Cu(I)/TEMPO system, a Cu^I resting state was observed for activated alcohols and a mixed Cu^I/Cu^{II} resting state for aliphatic substrates. These conclusions fit with the data obtained in

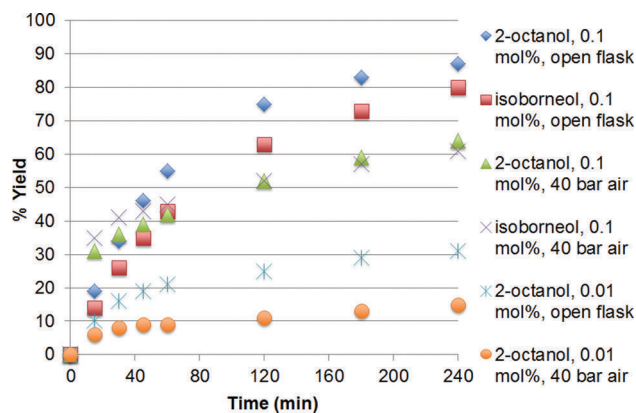


Fig. 9 Influence of gas pressure and composition on the oxidation of 2-octanol and isoborneol. Reaction conditions: 1 mmol of substrate in acetonitrile (5 mL), ketoABNO (X mol%), CuI (7.5 mol%), bpy (7.5 mol%), NMI (10.5 mol%), 25 °C, stir rate = 950 RPM. "open flask" = ambient air, pressurised reactions carried out in small reactors (see ESI†).

our studies. It can be seen that higher concentrations of O_2 can lead to a dramatic improvement in the rate for 1-phenylethanol (Fig. 8). In the case of aliphatic substrates we find that once outside the mass transfer regime, there are clear differences in reactivity between activated and unactivated substrates. We also found that using pressure to increase the O_2 concentration was not beneficial for aliphatic substrates (Fig. 9). This indicates that for these alcohols the oxidation of the substrate is significantly slower. As has been discussed,⁵ such substrates have a higher pK_a and stronger α -C-H bond, which contribute to slower substrate oxidation. For these aliphatic alcohols we found that better performance could be obtained using ambient air compared to higher pressures. We believe that this is a consequence of increased rates of copper co-catalyst decomposition due to a combination of higher O_2 and Cu^{II} concentrations.

As mentioned earlier, Steves and Stahl recently reported the use of ABNO using $Cu(MeCN)_4OTf$ as the copper source and ^{MeO}bpy as the ligand.¹⁵ We examined this catalyst system for the oxidation of 1-phenylethanol and 2-octanol using 1 mol% and 0.1 mol% ABNO. We found (see ESI† for details) that at the lower catalyst loadings, once again the difference in reactivity between activated and unactivated alcohols became clear. In comparison to our system the ABNO system reported by Steves and Stahl¹⁵ is somewhat faster. We also compared different combinations of ligands and copper salts for both ABNO and ketoABNO (see ESI† for details). We found that the ABNO $CuOTf/^{MeO}bpy$ system was the fastest and ABNO was faster than ketoABNO when combined with CuI and bpy. However, it is worth noting that CuI and bpy are significantly less expensive than $Cu(MeCN)_4OTf$ and ^{MeO}bpy . Furthermore, ketoABNO is arguably easier to prepare, as the synthesis of ABNO involves a Wolff-Kishner reduction.

Recovery of such radicals is desirable and the structure of ketoABNO means that it can be easily immobilised on to supports via a simple reductive amination (Fig. 10). This is an

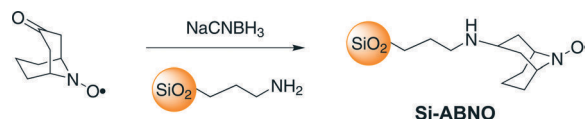


Fig. 10 Preparation of Si-ABNO.

approach that has been employed with 4-oxoTEMPO¹⁹ and in fact silica tethered TEMPO is a commercial product.^{7,19c}

We prepared Si-ABNO and found that it could effectively oxidise alcohols aerobically when combined with the copper co-catalyst (see ESI† for more details). However, the performance of the Si-ABNO catalyst was significantly decreased upon attempted recycles of the radical. Further investigations are needed to examine the reasons behind deterioration of catalytic performance. Prior studies with Si-TEMPO have used sodium hypochlorite¹⁹ or nitric acid²⁰ systems, therefore we need to assess if these problems are related to the copper system. Based on what we have observed with the homogeneous reactions, we believe that decomposition of the copper co-catalyst is likely to blame. As already mentioned, the copper co-catalyst is likely involved in the regeneration of the radical. Consequently, decomposition of the copper complex will lead to a reduction in the amount of radical. This may explain the decrease in performance with each successive run.

In summary, we have shown that a $Cu(I)$ /ketoABNO system can effectively oxidise secondary alcohols, with the radical demonstrating high turnover numbers and turnover frequencies. Trends in reactivity for activated and unactivated alcohols suggest similar behaviour to the $Cu(I)$ /TEMPO system. Preliminary results also demonstrate that ketoABNO can be easily tethered to silica gel and future work will be aimed at developing a recyclable solid supported ABNO catalyst system.

Acknowledgements

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Aerobic oxidation catalysis with stable radicals

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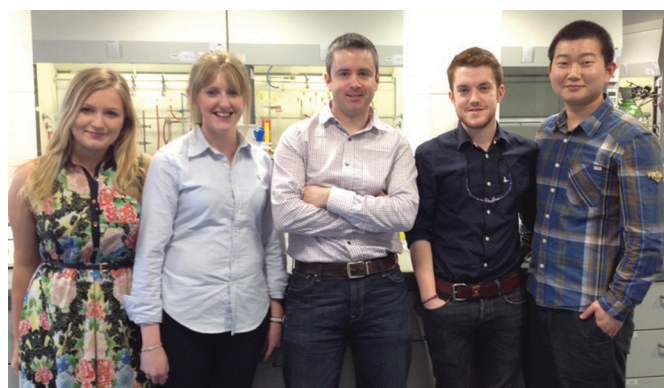
Selective oxidation reactions are challenging when carried out on an industrial scale. Many traditional methods are undesirable from an environmental or safety point of view. There is a need to develop sustainable catalytic approaches that use molecular oxygen as the terminal oxidant. This review will discuss the use of stable radicals (primarily nitroxyl radicals) in aerobic oxidation catalysis. We will discuss the important advances that have occurred in recent years, highlighting the catalytic performance, mechanistic insights and the expanding synthetic utility of these catalytic systems.

Introduction

Developing practical and sustainable catalytic methods for selective oxidation reactions is an important challenge. In the production of fine chemicals and pharmaceuticals, oxidations are often problematic. For example, in a study by leading

pharmaceutical companies which examined the reactions commonly used in the synthesis of drug candidates, it was found that oxidations were often avoided.¹ In their conclusions, the authors stated: “In contrast to reductions, there are relatively few atom efficient, chemoselective and environmentally acceptable oxidation methods. As a consequence, oxidations are often designed out of syntheses. The discovery of new chemoselective oxidations, particularly if catalytic, would greatly increase flexibility in synthetic design”.¹

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From Left to Right: Laura Dornan, Louise Hughes,
Mark Muldoon, Luke Rogan and Qun Cao

he carried out research in synthetic organometallic chemistry. He joined the Muldoon Group in September 2012 and his PhD studies are investigating aqueous oxidation reactions and the use of solid supported catalysts.

Louise obtained a 1st Class MSci degree in Chemistry from QUB in 2013. Her MSci research project was carried out in the Muldoon Group investigating the use of sterically unhindered nitroxyl radicals for aerobic oxidation catalysis. She commenced her PhD in the Muldoon Group in September 2013.

Mark obtained his BSc from the University of Strathclyde in Glasgow in 1998. He then worked as a process scientist for Boots PLC before returning to the University of Strathclyde for his PhD (1999–2003). He carried out postdoctoral research at the University of Notre Dame, Indiana, USA (2003–2005). From 2005–2007 he held a Ramsay Memorial Fellowship at the University of St Andrews. In 2007 he was appointed to a Lectureship in Inorganic Chemistry at QUB. His research interests are focused on catalysis, (particularly selective oxidation reactions), neoteric solvents and reaction engineering.

Qun obtained a BSc in Chemical Engineering and Technology from the China University of Mining and Technology in 2011. He is carrying out his PhD in the Muldoon group, developing catalytic methods for a number of different oxidation reactions.

Laura obtained a 1st Class MSci degree in Chemistry from Queen's University Belfast (QUB) in 2012. Her MSci research project was carried out in the Muldoon Group investigating Cu/TEMPO catalysis for the oxidative synthesis of nitriles. She was the recipient of a Nuffield Undergraduate Research Bursary in 2011 and in 2013 she carried out an internship at Genentech in San Francisco. She is carrying out her PhD in the Muldoon Group exploring new methods for selective oxidation catalysis.

Luke obtained a 1st Class BSc degree in Chemistry with Extended Studies in Europe from QUB in 2012. During his undergraduate studies he spent a year at the University of Zaragoza in Spain, where



In terms of sustainability, O_2 is the ideal terminal oxidant. It is readily available and H_2O is usually the by-product of catalytic oxidation reactions. The importance of developing better aerobic oxidation catalysts means there is now an increasing emphasis on this challenge and it is becoming a fast moving research area. A plethora of metal catalysts (both homogeneous and heterogeneous) have been reported for a wide range of oxidation reactions; ranging from alcohol oxidation to C–H bond functionalisation.²

In this review we will concentrate on the use of stable radical catalyst systems. We believe these catalysts have attributes that make them viable for larger scale applications. It is common strategy that these stable radicals are combined with metal co-catalysts and these are normally first row transition metals such as copper and iron. Although platinum group metals such as Pd, Pt, Ru and Ir have a long history in oxidation catalysis, these metals are expensive and the cost of such metals is only likely to get higher. Recently the British Geological Society published a report on the “supply risk” for chemical elements,³ and platinum group metals were identified as high risk elements. In contrast, copper and iron were rated as very low risk. Platinum group metals are also substantially more toxic than copper and iron and their presence in pharmaceutical and dietary products must be kept to very low levels.⁴ Platinum group metals are “Class 1 metals: metals of significant safety concern”, while copper comes under “Class 2 metals: metals of low safety concern” and iron is under “Class 3 metals: metals of minimal safety concern”.⁴ Furthermore, catalysts based on copper and iron tend to have better tolerance of other functional groups and heteroatoms, unlike noble metal catalyst systems, which we will highlight later. This is an important trait when oxidations are required on poly-functionalised molecules. We will also give examples of stable radical catalyst systems that do not employ any transition metal co-catalysts.

In 2010, Ciriminna and Pagliaro reviewed some of the recent industrial oxidation processes that utilise the stable radical 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) and its derivatives.⁵ In this review, only one of the industrial examples was aerobic and the rest all utilised Anelli–Montanari⁶ type conditions. In this method the oxoammonium salt of TEMPO carries out alcohol oxidation and hypochlorite is added in excess (Fig. 1). Although this approach can be very effective, hypochlorite

(i.e. bleach) is not compatible with certain chemicals, for example ammonia (see nitrile synthesis later). An additional problem is that this method can result in unwanted chlorinated by-products.⁷ Consequently, there are some important drivers for moving towards halide free systems which use O_2 as the terminal oxidant.

Scope of the article

This review will focus on recent advances in aerobic oxidations using stable radicals as catalysts for applications in synthetic chemistry. In most cases the radicals in question will be nitroxyl radicals; however there are a few examples that involve other classes of stable radical. It is worth mentioning some preceding manuscripts in this area. In 2004 and 2006 Sheldon and Arends published reviews on the use of nitroxyl radicals for catalytic oxidations.⁸ In 2009, Bobbitt *et al.* reviewed the use of nitroxides and oxoammonium salts for the catalytic oxidation of alcohols.⁹ In 2011, Tebben and Studer published a review on the use of nitroxide radicals for a range of applications in synthesis and in polymer chemistry.¹⁰ Wertz and Studer recently published a review on transition-metal-free nitroxide-catalysed systems which covers both stable and non-persistent radicals.¹¹ Very recently, Allen *et al.* published an all-encompassing review on copper catalysed aerobic oxidations (discussing the literature up to 2011), and this examined a significant number of copper/TEMPO studies.^{2h} A book published by Hicks (ed.) discusses in detail many aspects of stable radicals and their chemistry.¹²

We are focused on *stable* radicals and as such will not discuss the use of *N*-hydroxyphthalimide (NHPI) which is used to generate the nitroxyl radical phthalimide-*N*-oxyl (PINO). The PINO radical (and similar analogues) have been utilised for a range of aerobic oxidation reactions. PINO has been shown to be more reactive than TEMPO, however, it is not stable and is usually formed from NHPI *in situ* by means of an initiator. Consequently this falls outside the remit of this article; however it has been reviewed elsewhere¹³ and is discussed in some of the reviews already mentioned.^{8,10,11}

The use of stable radicals in catalysis is an area that has gathered momentum in the last few years and as is appropriate in such a short review, we will concentrate on recent developments to avoid repetition of the discussions in these excellent earlier articles. Alcohol oxidation has received the most attention to date and we will therefore cover this important fundamental reaction in more detail, also outlining the latest mechanistic insights. Stable radical catalysts are increasingly being utilised for a variety of different oxidation reactions and we will highlight some of the new applications that are emerging.

Unhindered nitroxyl radicals

At this point it is worth introducing unhindered nitroxyl radicals as these will be discussed in later sections. The majority of studies have focused on the use of TEMPO, which is undoubtedly the most well-known and well-studied stable radical. Recently the use of sterically unhindered nitroxyl

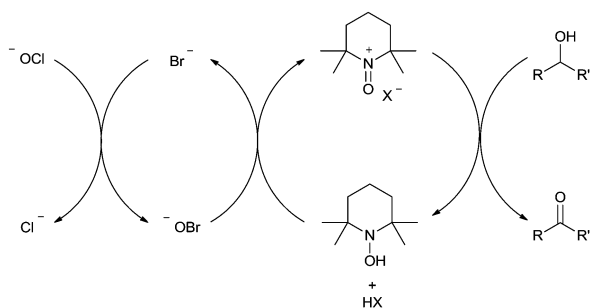


Fig. 1 Anelli–Montanari protocol where oxidation of the alcohol takes place via the oxoammonium salt.



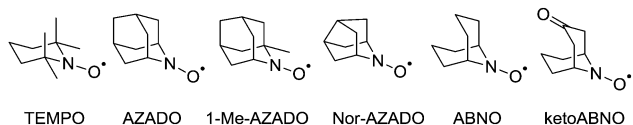


Fig. 2 Structural comparison of nitroxyl radicals. From left to right: 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), 2-azaadamantane *N*-oxyl (AZADO), 1-methyl-2-azaadamantane *N*-oxyl (1-Me-AZADO), 9-azanoradamantane *N*-oxyl (Nor-AZADO), 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO), 9-azabicyclo[3.3.1]nonan-3-one *N*-oxyl (ketoABNO).

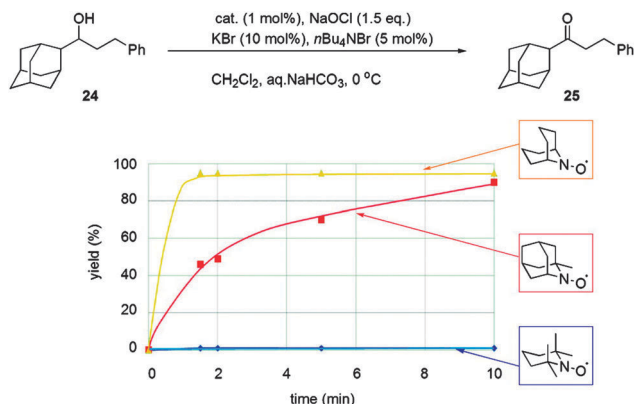


Fig. 3 Illustration of how steric hindrance between radicals and substrates affects reactivity using the Anelli–Montanari protocol. Reproduced with permission from ref. 19b © 2009 American Chemical Society.

radicals has emerged. Such radicals have been known since the 1960s¹⁴ but until recently they have not been exploited for oxidation catalysis. Unlike TEMPO, unhindered radicals such as those shown in Fig. 2 possess α -hydrogens but are still stable, as they are protected from disproportionation (to the hydroxylamine and a nitron), because the resulting double bond would form at a bridgehead, violating Bredt's rule.¹⁵

These types of radicals were initially examined in fundamental physical-organic studies, and it has been known for some time that ABNO is more reactive than TEMPO.¹⁶ However, only recently have these radicals been used for oxidation chemistry in the same manner as TEMPO. Early oxidation studies used electrochemical methods,¹⁷ trichloroisocyanuric acid¹⁸ or bleach¹⁹ as the oxidant to generate the oxoammonium salt. It was shown that such unhindered radicals could carry out oxidations faster than TEMPO and, perhaps, more importantly, they could oxidise sterically hindered alcohols that TEMPO could not. Fig. 3 illustrates the ability of ABNO to efficiently oxidise a bulky alcohol compared to TEMPO (and 1-Me-AZADO) using Anelli–Montanari conditions.

The use of these stable radicals for *aerobic* oxidation catalysis has now been reported for a number of different applications and we will discuss these in the relevant sections below.

Alcohol oxidation

Alcohol oxidation is a fundamental reaction in organic chemistry, and while traditional methods may be trivial to use on a

small scale, this reaction poses a real challenge when it has to be carried out on an industrial scale.¹ There has therefore been a considerable amount of effort put into developing sustainable aerobic catalytic methods for this reaction. We believe that the use of stable radicals for aerobic alcohol oxidation has emerged as a very promising approach. Nitroxyl radicals are often combined with first-row transition metal co-catalysts, although the use of nitrites or nitric acid to produce NO_x , which then acts as a co-catalyst, is also a method that is showing great promise.

Copper

The first example of aerobic alcohol oxidation using copper and a nitroxyl radical was reported in 1966.²⁰ Brackman and Gaasbeek combined di-*tert*-butylnitroxyl with a copper(II) phenanthroline complex for the oxidation of methanol. However, the most well-known and widely studied system employs copper complexes combined with TEMPO, which was first reported by Semmelhack and co-workers in 1984.²¹ Since that report, numerous studies have explored this catalyst system, investigating ligands,²² neoteric solvent systems,²³ immobilisation,²⁴ reaction engineering²⁵ and oxidation of renewable substrates.²⁶ However, we wish to focus on the recent reports, primarily from the Stahl Group, which exemplify the potential of Cu/nitroxyl catalysis for synthesis and also give further mechanistic insights. Prior to discussing these papers we want to highlight some seminal studies that shaped the development of this catalyst system.

The original Semmelhack study combined TEMPO with CuCl using DMF as the solvent and O_2 bubbling through the system.²¹ This catalyst system could oxidise 1° benzylic and allylic alcohols at 25 °C, but was not effective for aliphatic alcohols. It was shown to preferentially oxidise 1° over 2° alcohols. Later, Sheldon and co-workers developed a system which utilised Cu(II) salts, 2,2'-bipyridine (bpy) as a ligand and *t*-BuOK as a base in a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (2 : 1) solvent mixture.²⁷ This catalyst system was able to carry out oxidations at 25 °C using ambient air as the source of O_2 . For activated alcohols, high yields of product were obtained in 2–5 hours using 5 mol% catalyst loadings. In order to obtain a high yield for an unactivated primary alcohol (1-octanol) the reaction required heating at 40 °C for 24 hours with a higher loading of TEMPO (7.5 mol%). This catalyst was also found to be selective for primary alcohols. Kinetic studies^{27b,c} led the authors to suggest that the reaction mechanism may have similarities to that of the copper protein galactose oxidase,²⁸ with TEMPO playing the role of the protein-bound phenoxyl radical. This suggestion of a copper-centred dehydrogenation differed significantly from the 'oxoammonium' type mechanism previously proposed by Semmelhack.²¹

The catalyst system was further improved by Kumpulainen and Koskinen.²⁹ They carried out kinetic studies, investigating the effects of the different components in the system. Bpy was used as the ligand along with Cu(II) salts to explore the effect of the base in detail. It was found that better performance could be obtained using organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and *N*-methylimidazole (NMI). They also found that



pure acetonitrile gave the best results (as opposed to an aqueous mixture). Kinetic studies found a first-order (1.15) kinetic correlation for TEMPO and a second-order correlation (2.25) for copper, which supported the idea that a binuclear copper intermediate was formed during the reaction. The optimised system demonstrated improved reactivity and could oxidise aliphatic alcohols in good yields at room temperature. Utilising 3 mol% Cu(OTf)₂, bpy, TEMPO, NMI and DBU, 1-decanol could be oxidised to almost complete conversion in 5 hours. With the addition of 3 Å molecular sieves to remove traces of water, complete conversion was achieved in 3 hours with 95% isolated yield. These reactions were carried out under an atmosphere of O₂ (balloon), although during their kinetic studies (which focused on *trans*-2-hexen-1-ol as a model substrate) they showed that the use of air only decreased the rate slightly. This more reactive system could oxidise secondary aliphatic alcohols, albeit at a higher temperature (40 °C) and longer reactions times (59% conversion in 48 hours).

In 2011, Hoover and Stahl reported that Cu^I salts were superior to Cu^{II} salts in a system which used NMI as a base.³⁰ It can be seen in Fig. 4 that Cu(I) salts in conjunction with bpy and NMI in pure acetonitrile resulted in improved reactivity.

This study also demonstrated that Cu/TEMPO can oxidise a wide range of substrates and is tolerant of many functional groups. Fig. 5 shows a sample of the substrate scope for this system. As part of their studies they examined how the Cu(I)/TEMPO system compared to other homogeneous oxidation catalysts. Pd(OAc)₂/pyridine and RuCl₂(PPh₃)₃/TEMPO systems were tested, which showed that these precious metal catalysts struggled to oxidise substrates containing alkene, alkyne, ether, sulphur and nitrogen functionalities.

As we have mentioned, Cu/TEMPO systems are often selective for primary alcohols over secondary alcohols. This study

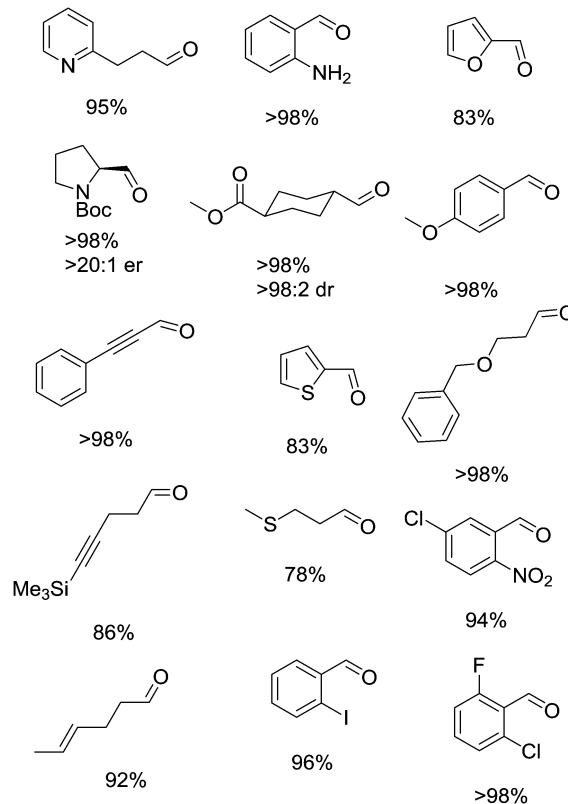


Fig. 5 Examples of the carbonyl products that can be produced using (bpy)Cu(I)/TEMPO (5 mol%) and NMI (10 mol%) in CH₃CN.

also looked at the chemoselectivity using a number of different diol substrates, studying both steric and electronic effects (*i.e.* benzylic *vs.* aliphatic). It was shown that it is possible to obtain selectivity for 1° over 2° for a variety of alcohols. In some cases, the (bpy)Cu(OTf)/TEMPO/NMI system was too reactive and improved selectivity was obtained by varying the choice of copper salt or base. For example, in the case of 1° benzylic *vs.* 2° benzylic substrates, Cu(I) salts were too active and also oxidised the 2° alcohol group to the ketone. Using the less reactive CuBr₂ allowed selective oxidation of only the 1° alcohol. In other cases, switching from Cu(OTf) to CuBr was sufficient to improve the selectivity.

They also discussed the limitations of the catalyst, highlighting a number of problematic substrates. It was found that homobenzylic substrates were over-oxidised with oxygenation occurring at the benzylic position. Terminal alkynes were found to produce a mixture of unwanted products. Substrates with the ability to chelate such as vicinal diols or those with adjacent heteroatoms (*e.g.* 2-pyridinemethanol) led to very low conversions. Substrates with a phenol substituent were also shown to be unreactive. In these cases it would seem that the substrates bind to the Cu and form unreactive complexes.

In most cases, substrates could be oxidised at room temperature using ambient air ("open flask"). This makes this method³¹ very safe and accessible to those wanting to use it on a small scale; indeed it has even been shown to be suitable as an undergraduate laboratory experiment.³² On a larger scale,

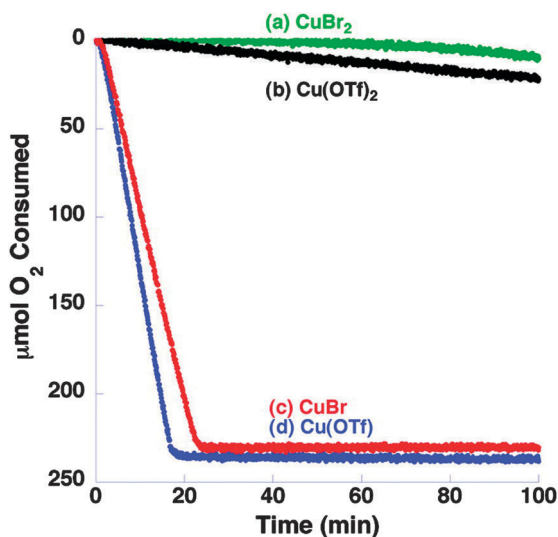


Fig. 4 Influence of Cu source on the oxidation of benzyl alcohol oxidation at 27 °C in CH₃CN using Cu source (5 mol%), bpy (5 mol%), TEMPO (5 mol%) and NMI (10 mol%). Reproduced with permission from ref. 30 © 2011 American Chemical Society.

this “open flask” approach is obviously not practical. In industry it is common practice to use dilute oxygen mixtures (e.g. <10% O₂ in N₂) so that the gas mixture is essentially non-flammable. The most scalable approach would be to operate under continuous flow conditions. Stahl and co-workers have recently published a report demonstrating the use of Cu(I)/TEMPO for alcohol oxidation under continuous flow conditions.³³ In this case the system used 35 bar of 9% O₂ in N₂ and they heated a tubular reactor to temperatures up to 100 °C. High yields of aliphatic aldehydes could be obtained with residence times from 30–45 min, while activated alcohols only required residence times of ≤5 min. In the case of benzyl alcohol to benzaldehyde they demonstrated the reaction on a larger scale to produce 100 g of product.

The initial Cu(I)/TEMPO studies by Stahl and co-workers focused on the substrate scope and methods. This was followed up in 2013 with mechanistic studies for this catalyst system.^{34,35} These studies are the most comprehensive mechanistic studies to date with a range of techniques employed to help propose a mechanism. Gas chromatography, gas-uptake, *in situ* IR, cyclic voltammetry, EPR and UV-visible spectroscopy were all utilised and detailed studies of the kinetic isotope effect were carried out. The catalytic cycle they proposed is shown in Fig. 6.

Both activated (benzyl alcohol) and unactivated (cyclohexylmethanol) substrates were examined and it was found that these different classes of substrate had different turnover-limiting steps. In the case of benzyl alcohol (which is easier to oxidise) they found that oxidation of the catalyst by O₂ was the limiting step. As can be seen in Fig. 6, catalyst oxidation is proposed to occur *via* a binuclear Cu₂O₂ intermediate. In the case of the unactivated substrate, cyclohexylmethanol, it was found that both substrate oxidation and catalyst oxidation affected the rate. It is a general phenomenon that aliphatic alcohols are more difficult to oxidise and many catalysts struggle with such substrates, even under more forcing conditions. In the

case of this Cu/TEMPO system the pK_a of aliphatic alcohols means that the formation of Cu-alkoxide species will form less readily and the bond strength of the α-C–H bond is significantly greater for aliphatic alcohols; which will clearly affect the product forming step(s). In this mechanism it is proposed that hydrogen atom abstraction (from the α-C–H) occurs *via* a bimolecular reaction between the Cu-alkoxide and TEMPO. In this study they found no evidence of a Cu–TEMPO adduct being involved in this step; which is in agreement with another recent study by Bonnet and co-workers.³⁶ As we mentioned earlier, oxoammonium salts have been proposed as active species in Cu systems, however in this Cu(I)/TEMPO study they utilised cyclic voltammetry and EPR to show that Cu(II) could not oxidise TEMPO to its oxoammonium (TEMPO⁺) ion under the reaction conditions.

As outlined earlier, there are a number of closely related Cu/TEMPO systems (*i.e.* Semmelhack, Sheldon, Koskinen and now Stahl). In the second mechanistic report by the Stahl group,³⁵ they examined the differences between these systems. The influence of ligand, solvent, base and Cu source were studied, giving further mechanistic insights into the effect of these components. Worth highlighting here is the reason for the rate acceleration found when Cu^I (rather than Cu^{II}) salts are employed with NMI as the base. It is believed that the *in situ* formation of a hydroxide base (step 4 in Fig. 6) allows the Cu^{II}-alkoxide species to be readily formed. In this system, it appears as though NMI may be acting as a ligand. If a Cu^{II} source is used, such a Cu hydroxide species is not formed and it is necessary to add a stronger base (e.g. DBU) in order to obtain a fast reaction. Cu^IOTf/NMI and Cu^{II}(OTf)₂/DBU may have similar efficiencies, however the authors point out that using a system with a weaker base (*i.e.* NMI) can be very useful in some cases, as strong bases can lead to epimerization of stereocentres.

Although we have only highlighted these recent studies, there have been a variety of mechanisms and variations of mechanisms suggested for Cu/TEMPO catalysed alcohol oxidation.^{27,29,37–40} Of course, it is possible that a number of variations are feasible and different pathways will depend on the reaction components and conditions. Nonetheless, such mechanistic studies are extremely valuable as the insights they provide can lead to the design of better catalysts. Indeed, very recently copper based systems were further improved by utilising such mechanistic understanding. As already discussed, the Cu/TEMPO systems allow primary alcohols to be selectively oxidised in the presence of secondary alcohols. While this may be a significant advantage in some cases, the oxidation of secondary alcohols is often desired and Cu/TEMPO is not a suitable catalyst. One of the reasons for the poor performance of secondary alcohols is believed to be due to steric hindrance (as secondary alcohols are bulkier) and the final step in the mechanism involves a bimolecular reaction between the Cu-alkoxide and TEMPO. It was recently shown by Steves and Stahl that this can be addressed by switching from TEMPO to the sterically unhindered nitroxyl radical ABNO.⁴¹ The optimised system consisted of 5 mol% Cu(MeCN)₄OTf, 5 mol%

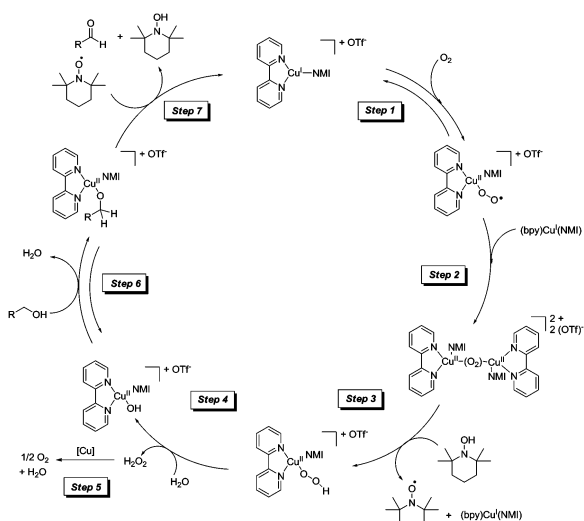


Fig. 6 Catalytic cycle for Cu/TEMPO aerobic oxidation of alcohols.³⁴



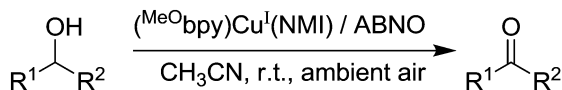


Fig. 7 Cu^I/ABNO aerobic oxidation of alcohols.

4,4'-dimethoxy-2,2'-bipyridine (^{MeO}bpy), 10 mol% NMI and 1 mol% ABNO (Fig. 7).

The Cu(I)/ABNO system can effectively oxidise a wide range of secondary alcohols, including substrates with bulky groups close to the alcohol group, such as 2,2-dimethyl-3-octanol, menthol and 2,2-dimethyl-1-phenyl-1-propanol. Using the conditions described, high isolated yields of product could be obtained in just 1 hour in most cases. As might be expected, the catalyst can still oxidise primary alcohols and has a similar functional group tolerance to that of Cu/TEMPO, with similar limitations also (e.g. terminal alkynes, phenols and primary homobenzylic alcohols).

Although the Steves and Stahl study⁴¹ included some amino functionalised substrates, very recently Iwabuchi and co-workers reported the use of Cu/AZADO for the oxidation of a wide range of unprotected amino alcohols (Fig. 8).⁴² In initial optimisation experiments they found that a number of unhindered radicals were far superior to TEMPO. From these studies the Cu/AZADO system was chosen and explored for the oxidation of a wide range of substrates, with AZADO loadings of 1–5 mol% used. It was demonstrated that along with tertiary amines, substrates containing primary and secondary alcohols could also be oxidised in good to excellent yields. They compared the AZADO catalyst system to traditional oxidation methods (pyridinium chlorochromate, Swern, Dess–Martin periodinane and tetrapropylammonium perruthenate) for a number of model substrates and found that the AZADO system could deliver better yields. Furthermore, they synthesised two natural products (myosmine and (–)-mesembrine), which are prepared by the oxidation of amino alcohol precursors. In these cases, higher catalyst loadings were required (10 and 15 mol% respectively), however it does highlight the potential of these catalyst systems.

Iron

A number of publications have reported aerobic Fe/TEMPO systems for catalytic alcohol oxidation. The exact nature of the catalyst often varies and an assortment of iron salts and TEMPO derivatives have been reported;^{43–47} but there are some general trends. Iron(III) salts are normally employed and unlike Cu/TEMPO systems, Fe/TEMPO catalysts don't usually require any base or organic ligands. The best performance also appears to be obtained from weakly coordinating solvents (e.g. dichloroethane)

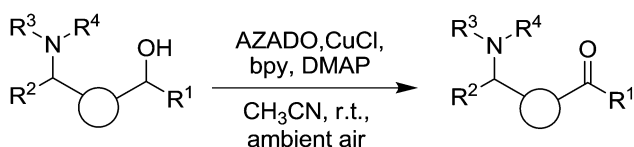


Fig. 8 Cu^I/AZADO aerobic oxidation of amino alcohols.

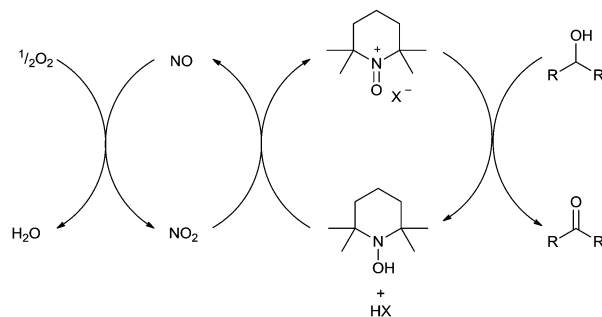


Fig. 9 Aerobic oxidation of alcohols via the oxoammonium cation coupled with NO_x.

unlike Cu/TEMPO which normally uses acetonitrile. The substrate scope for these catalysts is also very good and can tolerate alkenes, alkynes and heteroatoms. It is fair to say that Fe/TEMPO systems have not yet been subjected to detailed mechanistic studies, so the exact mechanism(s) is still open to conjecture. Recent studies with MCl₃(η¹-TEMPO) (M = Fe, Al) showed that these complexes can oxidise alcohols,⁴⁸ although the majority of *catalytic* studies utilise Fe(NO₃)₃ as the iron salt or use NaNO₂ as an additive. It is therefore likely that NO_x is playing a key role in these systems and this has been suggested by some authors.^{43,47} It has been known for some time that NO₂ can oxidise nitroxyl radicals such as TEMPO to their oxoammonium salts (Fig. 9),⁴⁹ so this is certainly a very plausible explanation for the use of nitrate salts or nitrite additives. It has also been suggested that NO₂ could also assist in the re-oxidation of Fe(II) to Fe(III).⁴⁷

Unlike the Cu/TEMPO system, Fe/TEMPO readily oxidises secondary alcohols. This could be because the oxoammonium salt is the active oxidant, although arguably even if iron/TEMPO did work in unison, one might not expect the same preference for primary alcohols. Fe/TEMPO systems do not require an additional ligand (such as bpy) and therefore they are sterically less hindered compared to Cu/TEMPO systems.

We will now highlight some of the more recent Fe/TEMPO papers. In 2011 Ma *et al.* improved the performance and substrate scope of previous Fe–TEMPO catalyst systems, by using NaCl as an additive.⁴⁷ The optimised components for room temperature alcohol oxidation were Fe(NO₃)₃·9H₂O, TEMPO and NaCl using an oxygen balloon with 1,2-dichloroethane (DCE) as solvent. Some examples of the carbonyls that were prepared are shown in Fig. 10.

This Fe/TEMPO system readily oxidised standard model alcohols such as primary and secondary allylic, benzylic and unactivated aliphatic alcohols. A range of primary and secondary allenols were also oxidised without over-oxidation. The catalyst was tolerant of functional groups such as silyl ethers. Primary and secondary propargylic alcohols, including substrates with a terminal alkyne group, were oxidised. Fe/TEMPO systems are also tolerant of heteroatoms such as oxygen, sulfur and nitrogen. It is worth noting that in the case of nitrogen normally only pyridine type substrates have been shown in publications to date. We suspect that some amines may not be compatible due to the presence of NO_x. For example, anilines



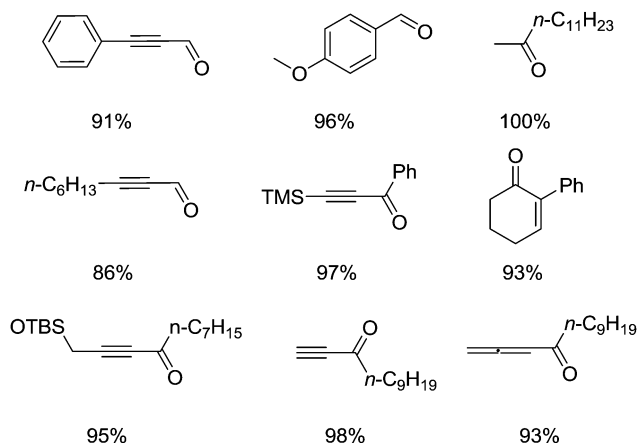


Fig. 10 Some examples of products produced by the $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ /TEMPO/NaCl system.

would likely lead to the formation of azo compounds (see later for such an example in a NO_x type system).

Using 1-phenylethanol as a model substrate this research group have demonstrated the reaction on a larger scale (4 mol) and also with air as the oxidant. Subsequently, they applied the $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ /TEMPO/NaCl/DCE catalyst system to the oxidation of indole-carbinols,⁵⁰ a range of propargyl alcohols,⁵¹ and allylic alcohols.⁵² In the latter case, they found that it was possible to produce the α,β -unsaturated enals and enones with retention of the C–C double-bond configuration.

Gao and co-workers recently reported two Fe/TEMPO catalyst system that utilise silica. Their first report was a rare example that did not use $\text{Fe}(\text{NO}_3)_3$ or NaNO_2 ; instead silica gel was coupled with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /TEMPO.⁵³ It was thought that the silica gel acted as a support for the catalyst. The optimised catalyst system used toluene as the solvent and a temperature of 80 °C. Reactions were carried out in a pressurised reactor and utilised either 5 bar of O_2 or air, with air requiring longer reaction times. The catalyst did not perform well for unactivated aliphatic alcohols. They then followed this study with a different silica based system which showed improved reactivity.⁵⁴ In this case TEMPO was covalently bound to a silica support and combined with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /NaNO₂. The heterogeneously supported TEMPO was prepared *via* reductive amination of 4-oxo-TEMPO with amine-functionalised SBA-15 (an approach to immobilise TEMPO that has previously been reported by Bolm and co-workers⁵⁵). Using benzyl alcohol as a model substrate the authors could achieve very efficient oxidation to benzaldehyde with a loading of just 0.01 mol% of the heterogeneous radical, with 8 mol% $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and 10 mol% NaNO₂, in toluene and O_2 (1 atm) at 25 °C. TEMPO is clearly the most expensive part of these catalyst systems and in this study they not only showed that reduced loadings of TEMPO could be used but that the catalyst could also be recycled. For benzyl alcohol oxidation both the iron salt and heterogeneous TEMPO were recycled together (5 runs). They also showed that SBA-15-TEMPO could be recycled on its own (*i.e.* with fresh $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and NaNO₂) and used for 10 reactions

without significant loss in activity or selectivity for the benzaldehyde product. The oxidation of a range of substrates was shown with loadings of SBA-15-TEMPO from 0.1 to 1 mol%. This catalyst system had enhanced performance for unactivated substrates, although primary aliphatic alcohols were not converted as readily as secondary aliphatic alcohols. The authors also demonstrated for a series of alcohols that atmospheric air could be employed, albeit with longer reactions times.

Obermayer *et al.* described a continuous flow approach employing a microreactor.⁵⁶ In this case, the Fe–TEMPO system comprised of a heterogeneous iron oxide nanoparticle catalyst stabilised on a mesoporous aluminosilicate support, with TEMPO dissolved in solution and flowed through the reactor. The oxidation of benzyl alcohol to benzaldehyde was used as a model reaction. It was found that the activity of the Fe/Al-SBA-15 nanoparticle catalyst (1 wt% Fe) was enhanced by the addition of TEMPO. They could achieve a yield of 42% benzaldehyde in a single pass of the reactor, however compared to many of the systems we have discussed, the reaction conditions were rather harsh; 120 °C and 35 bar of pure oxygen. Nonetheless, this illustrates an important feature of using continuous flow microreactor systems; they enable reaction conditions to be employed that would otherwise be very unsafe. Indeed, we believe that such reaction engineering solutions will be central for aerobic reactions to be used industrially.

Cobalt and manganese

The use of cobalt and manganese co-catalysts with TEMPO and its derivatives has been known for some time.^{57–61} These studies have utilised nitrate salts, often employing the combination of both Co and Mn salts and using acetic acid as the solvent. The conditions would suggest that in these reactions the substrates are oxidised by the oxoammonium salt. Although there have not been extensive substrate scope studies, these catalyst systems can oxidise both secondary and primary alcohols and can convert unactivated aliphatic substrates; although secondary aliphatic alcohols require longer reaction times than their primary counterparts. There have also been reports with heterogeneous Cu/Mn oxide co-catalysts which do not employ acidic solvents.^{62–64} In these cases, low loadings of TEMPO were used and the heterogeneous catalyst was recycled, however the performance for aliphatic substrates was poor.

More recently, Zheng and co-workers demonstrated the use of cobalt as the sole metallic component in TEMPO-catalysed, aerobic alcohol oxidation with a $\text{Co}(\text{NO}_3)_2$ /dimethylglyoxime/TEMPO system.⁶⁵ It was found that weakly-coordinating solvents enabled the best performance with dichloromethane chosen as the optimum solvent. A temperature of 70 °C and 4 bar of O_2 was used in these studies. Activated substrates were converted with 1 mol% catalyst loadings and unactivated aliphatic alcohols (primary and secondary) could be oxidised with higher loadings (3 mol% Co and 5 mol% TEMPO).

Vanadium

There are fewer publications that employ vanadium co-catalysts, although the approach developed in 2001 by Neumann and



co-workers did make a real impact.⁶⁶ They reported the combination of TEMPO and the polyoxometalate, $H_5PV_2Mo_{10}O_{40}$ for the aerobic oxidation of alcohols. In this case, the polyoxometalate oxidises TEMPO to form the oxoammonium salt which then oxidises alcohols to their corresponding carbonyl compounds. It has also been reported that this catalyst system has been utilised industrially by DSM.⁵ Despite the fact that this system was used industrially, it has received little research interest (*cf.* copper and iron systems). In 2012, Lu and co-workers immobilised this polyoxometalate and an ionic liquid functionalised TEMPO on to silica-coated magnetic nanoparticles.⁶⁷ They demonstrated the oxidation of a range of alcohols and also showed that the catalyst could be separated (using an external magnet) and recycled 10 times without significant loss of activity.

Du *et al.* developed the first example of vanadium as the sole metallic component in TEMPO-catalysed alcohol oxidation with vanadyl sulfate ($VOSO_4$) (4 mol%) and TEMPO (4 mol%) in acetonitrile, O_2 (4 bar) at 80 °C.⁶⁸ The optimised catalyst system oxidised a range of primary benzyl alcohols, with electron-withdrawing substituents on the ring hindering the oxidation process. The secondary alcohol 1-phenylethanol was also easily converted to acetophenone. The catalyst did not perform well with secondary aliphatic alcohols which were only moderately converted; even with extended reaction times (primary aliphatic alcohols were not mentioned).

Laccase

This article mainly focuses on chemo-catalysis; however TEMPO (and derivatives) can be used in conjunction with laccase enzymes. Laccases (EC 1.10.3.2) are multi-copper-containing oxidases that can be used directly for the oxidation of anilines and phenols, or for a wider range of substrates when combined with electron transfer mediators. In 2001 it was shown that TEMPO could act as a mediator for the aerobic oxidation of alcohols.⁶⁹ It is believed that the mechanism of the laccase/TEMPO system involves the enzyme oxidising the nitroxyl radical to the corresponding oxoammonium cation, which then oxidises the alcohol.⁷⁰

Laccases have several industrial and biotechnological applications;⁷¹ however their potential in synthetic chemistry has been less explored compared to the aforementioned chemo-catalytic methods. More detailed discussion on prior work using laccases and mediators for synthetic chemistry can be found in earlier review articles,^{8,72} while we wish to highlight a very recent addition to the literature. Ying and co-workers reported the benefits of using unhindered nitroxyl radicals as mediators in combination with laccase (from *Trametes versicolor*).⁷³ In initial screening studies, they tested a range of conditions and nitroxyl radicals; however they primarily studied the use of AZADO. The main advantage of the laccase-AZADO system compared to TEMPO is that it vastly improves the reactivity towards sterically encumbered substrates, as exemplified in Fig. 11.

For unhindered substrates, there was little difference between AZADO and TEMPO, however for bulkier substrates a significant difference in performance was observed. For example, in the case

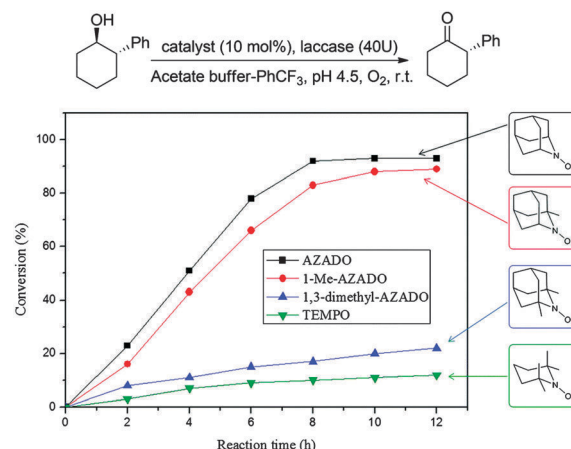


Fig. 11 Steric influence of nitroxyl radicals for laccase-nitroxyl catalysed oxidation of alcohols. Reproduced from ref. 73.

of menthol, a yield of just 5% was obtained in 36 hours using TEMPO, while AZADO delivered a yield of 84% in 12 hours. They demonstrated that laccase-AZADO could be used for very bulky substrates, including 1-(4-(benzyloxy)-2,6-dimethoxy-3,5-dimethylphenyl)-2-methylbutan-1-ol, which is a precursor for the synthesis of natural products wasabidienone B₁ and wasabidienone B₀. The system was able to tolerate a range of functional groups, although it did have a few limitations. Laccase oxidised the -OH and -NH₂ functionalities in phenol and aniline derivatives leading to the formation of unwanted side products. The system can tolerate thioethers, although substrates with free thiol groups (R-SH) were problematic, as these inhibit laccases.

NO_x oxidation systems

The ability to carry out catalytic reactions without the use of any transition metals has a number of potential advantages. For example, as discussed earlier for copper systems, phenols or substrates with chelating ability can bind to the metal and hinder the reaction. There are a number of reports of transition-metal-free aerobic systems with nitroxyl radicals. In these systems, it appears that the oxoammonium salt carries out substrate oxidation and NO₂ regenerates the oxoammonium salt. NO_x can be generated *in situ* from nitric acid, nitrates, nitrites or hydroxylamine. As we have already discussed NO₂ can readily oxidise nitroxyl radicals to their oxoammonium salts (Fig. 9); however in many of the earlier reports, halides were present suggesting that in such cases bromine, hypobromous acid, nitrosyl bromide or nitrosyl chloride could be acting as active co-oxidants.⁷⁴ There are clearly similarities between how these systems might operate and the bleach based (*i.e.* Anelli-Montanari protocol) systems. As mentioned earlier, an issue with such oxidations is that for some substrates there can be selectivity issues (*e.g.* halogenated by-products). Thankfully, it is possible to operate aerobic NO_x systems under halide-free conditions, which avoids such problems.⁷⁵

Early work with NO_x systems focused on TEMPO derivatives and although Kakimoto had shown that unhindered radicals such as AZADO resulted in faster reactions, their study still



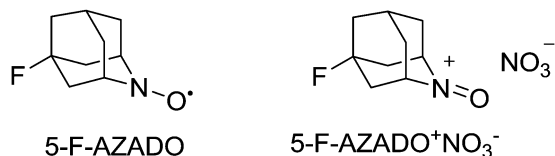


Fig. 12 5-F-AZADO and the corresponding oxoammonium nitrate salt.

focused on TEMPO.^{75b} Iwabuchi and co-workers demonstrated that unhindered radicals could not only deliver improved reactivity but also a wider substrate scope for such NO_x systems.⁷⁶ They studied a number of AZADO derivatives and found that the best reactivity was obtained with 5-fluoro-2-azaadamantane *N*-oxyl (5-F-AZADO) (Fig. 12).

They postulated that the increased oxidation potential of 5-F-AZADO compared to AZADO is responsible for the superior reactivity. They also demonstrated that it was possible to oxidise a range of substrates, including bulky substrates, which TEMPO struggles to oxidise. Fig. 13 shows examples of some products that were prepared in this study.

Oxidations were carried out at room temperature and gave high yields in reasonable reaction times (typically a few hours). They also utilised air (balloon) as the terminal oxidant. In general it was shown that 5-F-AZADO (1 mol%) could be used with NaNO₂ (10 mol%) or the oxoammonium nitrate salt (5-F-AZADO⁺NO₃⁻) (Fig. 12) could be formed and used without NaNO₂, albeit with a higher catalyst loading (5 mol%). Acetic acid was generally used as the solvent, however, it was demonstrated that by using 5-F-AZADO⁺NO₃⁻ the reactions could be run in acetonitrile with either 2 equivalents of acetic acid or completely acid free; the downside being extended reaction times. A reaction with 5-F-AZADO in dichloromethane was achieved when *tert*-butyl nitrite (*t*-BuONO) was employed. They also showed that it was

also possible to precipitate 5-F-AZADO⁺NO₃⁻ at the end of the reaction (72% was recovered) with the recovered salt showing the same reactivity in a subsequent reaction. Indeed, around a similar time, Kakimoto and co-workers reported how 1-methyl-2-azaadamantane *N*-oxyl (1-Me-AZADO) could be recycled.⁷⁷ This radical was used in conjunction with NaNO₂ and HNO₃ and the salt 1-Me-AZADO⁺NO₃⁻ was separated from the organic (product) phase due to its water solubility and then re-used.

More recently Lauber and Stahl studied the use of ABNO and ketoABNO for such NO_x type systems.⁷⁸ Although the previous work using AZADO based radicals demonstrated good performance, this more recent study was motivated by the fact that ABNO based radicals are significantly easier to prepare. In this study they initially prepared a range of ABNO derivatives, many of which had not been reported previously. These ABNO based radicals were then compared along with a number of TEMPO derivatives for their ability to oxidise cyclohexanol. It was found that ABNO and ketoABNO delivered the best performance in these screening tests. Interestingly, the results did not show a correlation between redox potential and catalytic performance. The authors said efforts to understand the factors behind good catalyst performance were underway, but suggested that in some cases the derivatives may not be as stable under the reaction conditions. In this study, they then examined ABNO and ketoABNO for a range of substrates, using three different methods. (Fig. 14)

Excellent yields could be obtained for a range of functionally diverse substrates. Method A gave the best performance overall, being applicable to the widest range of substrates, although in some cases Method C delivered higher yields. Although they demonstrated that these nitroxyl NO_x systems have excellent substrate scope, they also highlighted that there are some limitations. For example aniline derivatives are not suitable as the conditions may lead to the formation of diazo compounds. They also found that tertiary amines could be low yielding and a possible explanation for this was that such substrates could react with the acids that are utilised in these methods.

There are a number of papers which have looked at immobilising radicals for NO_x systems to facilitate the recycling of the radical. Zhu *et al.* utilised a TEMPO functionalised ionic liquid with NaNO₂ and the radical could be separated and recycled.⁷⁹ As part of their studies examining a system which used NH₄NO₃ as the source of NO_x, Stavber and co-workers employed a commercially available polymer-supported form of

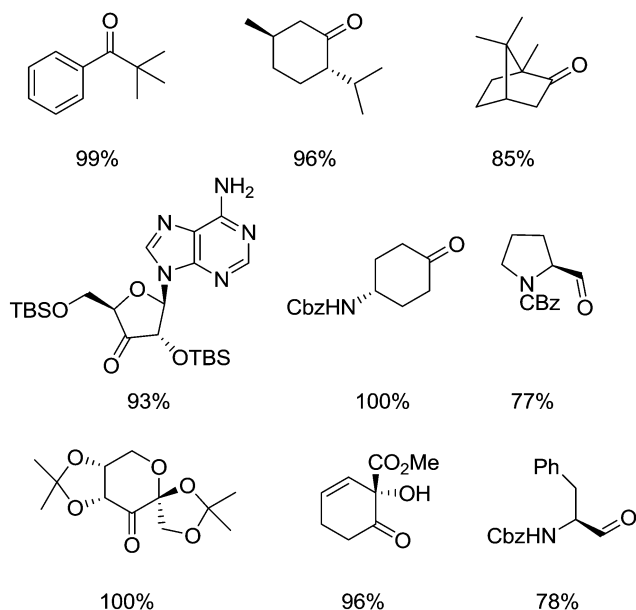


Fig. 13 Examples of some products produced via alcohol oxidation using 5-F-AZADO/NaNO₂/air or 5-F-AZADO⁺NO₃⁻/air.

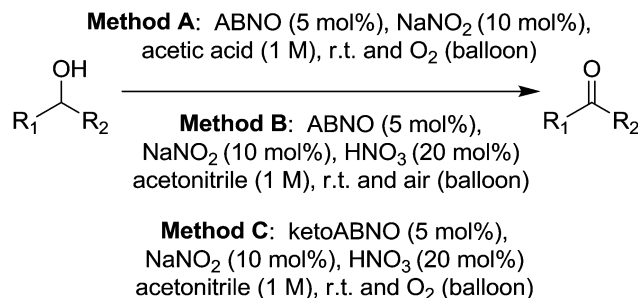


Fig. 14 Methods for alcohol oxidation using ABNO or ketoABNO.



TEMPO, enabling the radical to be recycled.⁸⁰ Karimi *et al.* have developed recyclable systems that use TEMPO covalently tethered to mesoporous silica (SBA-15) in conjunction with either sodium nitrite⁸¹ or *t*-BuONO.⁸² They also reported a *t*-BuONO system with TEMPO supported on magnetic core-shell nanoparticles, which can be easily separated (magnetically) and re-used.⁸³ There have also been studies,⁸⁴ including mechanistic studies,⁸⁵ where NO_x gas has been adsorbed onto silica-tethered TEMPO and then used for alcohol oxidation.

The most efficient way to utilise such solid supported catalysts is to operate a continuous flow system, something that was recently reported by Hermans and co-workers.⁸⁶ They demonstrated the aerobic oxidation of alcohols using (commercially available) silica-immobilised TEMPO and with catalytic amounts of HNO₃ as the source of NO_x. As mentioned earlier, flow systems also offer improved safety and in this case 5 bar of O₂ was used. They demonstrated that this flow approach had superior space-time-yields (*i.e.* the product yield per unit of time and per reactor volume) compared to previously reported batch systems. The flow system was tested on a number of representative model substrates including aliphatic alcohols and renewable substrates (lactic acid and 5-hydroxymethylfurfural).

In summary, the recent developments in stable radicals for aerobic oxidation of alcohols are very promising. It has been shown that these systems have excellent substrate scope and tolerance of a wide range of functional groups. Each method has specific substrate limitations, but the correct choice of method should allow most substrates to be oxidised efficiently. The methods often employ very mild conditions and it has been shown in some cases that it is possible to combine these oxidation reactions with other reactions in a one-pot manner. For example, Christmann and co-workers have described the Cu(I)/TEMPO oxidation of *Z*-allylic alcohols or *E/Z* mixtures with concomitant isomerisation (by DMAP) to form (*E*)- α,β -unsaturated aldehydes.⁸⁷ They also demonstrated that alcohol oxidation followed by an organocatalytic intramolecular Diels–Alder reaction could be carried out in one-pot, while Jang and co-workers demonstrated that a Cu/TEMPO oxidation of allylic alcohols could be carried out in tandem with the enantioselective Michael addition using a chiral amine catalyst.⁸⁸ They also found that if TEMPO was added in larger quantities, an addition reaction took place, resulting in tandem oxidation/Michael addition/ α -oxyamination reactions. There are a number of examples utilising these catalyst systems for the Passerini reaction (Fig. 15).⁸⁹ This reaction involves the condensation of an isocyanide with an aldehyde or ketone and carboxylic acid. These studies demonstrated that aldehydes or ketones could be generated *in situ* from the oxidation of alcohols.

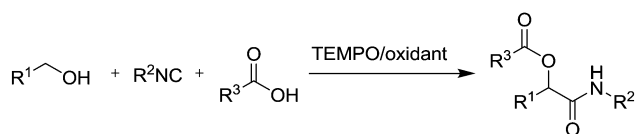


Fig. 15 Passerini reaction using alcohols.

In the studies we have highlighted, model substrates have been examined that are of relevance to applications in the fine chemical, pharmaceutical and agrichemical industries. A number of other studies have explored the oxidation of lignin and lignin model compounds, an important challenge if we are to exploit renewable resources for chemicals. These reactions involve alcohol oxidation and also C–C bond cleavage reactions. Hanson and co-workers have examined Cu/TEMPO catalyst systems,⁹⁰ while Stahl and co-workers examined a range of catalyst systems, focusing on the use 4-acetamido-TEMPO (4-AcNH-TEMPO) combined with HNO₃, and HCl as co-catalysts.⁹¹ The results from these studies are promising, and stable radicals may have a role to play in this extremely difficult challenge.

Expanding the scope of reactions

Although the majority of studies reported to date have examined alcohol oxidation, in recent years there has been a growing number of publications looking at other oxidative transformations. Herein we will highlight some of the recent developments involving stable radicals.

C–N bond formation

There have been a number of interesting reports of C–N bond forming reactions using TEMPO based catalysts. Zhang and Jiao reported a novel Cu-catalysed oxidative amidation–diketonisation reaction of terminal alkynes leading to α -ketoamides, in which molecular oxygen is used as both the oxidant and a reactant (Fig. 16).⁹² Labelling studies indicated the product oxygen atoms came from O₂ rather than H₂O. The reaction was mainly limited to activated substrates, for example an aliphatic alkyne was low yielding and aliphatic amines were unreactive.

More recently Chen and co-workers reported the use of iron nitrate/TEMPO for the preparation of amides from aromatic alcohols and amine hydrochloride salts.⁹³ This was a one pot, two-step procedure whereby Fe(NO₃)₃/TEMPO was used to carry out aerobic oxidation of the alcohol (limited to simple aromatic alcohols). Once the aldehyde was produced, the (aliphatic) amine hydrochloride salt was added along with CaCO₃ and *tert*-butyl hydroperoxide (TBHP). In this second step, it is believed that the oxidation of the hemiaminal is performed by Fe(III) and TBHP.

It is also worth mentioning a method that was reported in 2010 for the intermolecular C–H bond amination of acidic aryl C–H bonds with primary aromatic amines.⁹⁴ This was applied to electron-deficient polyfluoroarenes and polychloroarenes and azoles as shown in Fig. 17. The role of TEMPO was unclear,

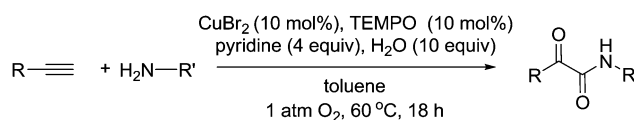


Fig. 16 The formation of α -ketoamides from aromatic amines and terminal alkynes.



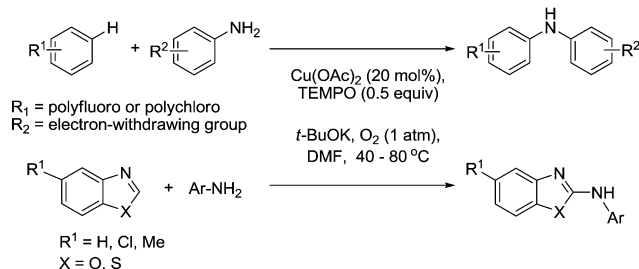


Fig. 17 Cu/TEMPO C–H bond amination.

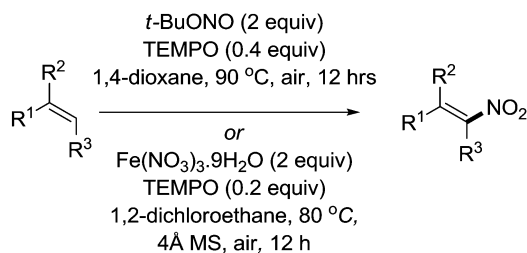


Fig. 18 Stereoselective nitration of olefins.

however its presence (at relatively high loadings) did improve the product yields.

Maiti and co-workers reported methods for the stereoselective nitration of olefins. In their first report, they combined TEMPO (0.4 equiv.) with AgNO_3 (3 equiv.) to carry out the nitration of a wide range of olefins with selectivity to the *E* isomer.⁹⁵ The method was then improved when they demonstrated that it was possible to avoid the use of silver salts (Fig. 18). First they showed that $\text{Fe}(\text{NO}_3)_3$ could be used,⁹⁶ then they reported a metal-free protocol using *t*-BuONO.⁹⁷

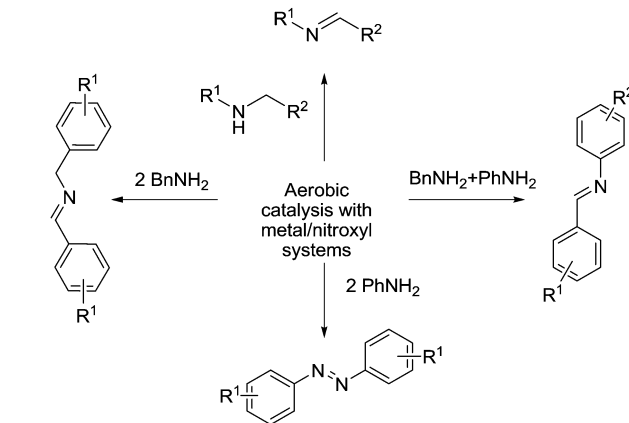
In these studies they demonstrated the utility of these methods for a wide variety of substrates: aromatic, aliphatic, hetero-aromatic and even substrates containing other alkene or alkyne functionality. In most cases, the products were obtained in good to excellent yields and had excellent *E* selectivity. Alkenes close to electron withdrawing groups reacted slower; therefore aliphatic terminal olefins could be selectively nitrated over a terminal alkene or indeed alkyne next to an ester group. There were also examples of substrates where a terminal olefin could be selectively nitrated in the presence of an internal olefin.

Maiti and co-workers also reported the (*E*)-nitroolefins *via* the decarboxylative nitration of α,β -unsaturated carboxylic acids, using *t*-BuONO (2 equiv.) and TEMPO (80 mol%).⁹⁸ It was shown that such reactions could proceed without TEMPO but a mixture of *E* and *Z* isomers were obtained, while TEMPO led to selective formation of the *E* isomer.

C=N bond formation

Synthesis of imines

Imines are versatile intermediates and can be used to prepare a variety of important chemicals. They are typically prepared

Fig. 19 General overview of the synthesis of imines and azo compounds via metal/nitroxyl/ O_2 catalysis.

from the condensation of amines with carbonyls (usually aldehydes). Oxidation catalysts can be used to make imines from alcohols and amines, in other words, generating the carbonyl *in situ* using an oxidation reaction. Imines can also be prepared *via* dehydrogenation of amines.⁹⁹ Fig. 19 outlines the ways in which metal/nitroxyl radical catalysts have been used for the synthesis of imines (and azo compounds).

In 2011, Xu and co-workers described a mild one-pot imine synthesis from alcohols and amines with $\text{Pd}(\text{OAc})_2$ and TEMPO.¹⁰⁰ The reaction proceeded without TEMPO however superior performance was obtained when the radical was present, although the reason for this is not clear.

In 2012, the same group reported that Cu/TEMPO could be used to prepare imines *via* this route. As discussed earlier, the replacement of Pd with Cu is desirable and it was found that Cu/TEMPO could be used to prepare a wide variety of structurally diverse imines in good to excellent yields.¹⁰¹ It also operated under very mild conditions; CuI (1 mol%), bpy (1 mol%) and TEMPO (2 mol%) in CH_3CN at room temperature and with an “open flask”. Although aldehydes react with amines to form imines in the absence of a catalyst, it was also shown in this paper that CuI accelerates this condensation reaction; consequently this one-pot approach from alcohols is a sensible route for the preparation of imines.

In 2011, Hu and Kerton demonstrated that $\text{CuBr}_2/\text{TEMPO}$ could be used to prepare imines from benzylamines under air at 25 °C in $\text{CH}_3\text{CN}-\text{H}_2\text{O}$.¹⁰² The catalyst could also be used for the oxidative coupling reaction between benzylamines and anilines at 45 °C. They also showed that electron donating anilines could undergo dehydrogenative coupling to form azo compounds in good yields at 60 °C. As discussed earlier, Cu(I) systems are more active for alcohol oxidation, and recently Xu and co-workers reported a copper(I)/TEMPO system for the oxidation of amines to imines under neat conditions (*i.e.* no additional solvent).¹⁰³ The same group also reported the use of $\text{Fe}(\text{NO}_3)_3/\text{TEMPO}$ for the synthesis of imines.¹⁰⁴ In this study they demonstrated that this catalyst could be used for the synthesis of imines *via* the oxidation of amines, the oxidation of alcohols with amines and also the oxidation of anilines with



benzylamines to form cross imines. They showed a broad substrate scope, however aliphatic substrates were not suitable for this catalyst system.

In 2012, Sonobe *et al.* published an excellent paper which described the synthesis of imines and their subsequent reactivity in C–C bond forming reactions.¹⁰⁵ This study utilised copper(I) complexes in combination with the sterically unhindered nitroxyl ketoABNO. Significantly this catalyst system was able to oxidise aliphatic amines and bulky amines that were previously not suitable when TEMPO was employed. It was clear that the utilisation of ketoABNO made possible reactions that could not be carried out using TEMPO. For example, they employed bulky ligands to ligate the copper and this would not have been suitable with the sterically hindered TEMPO. We will highlight the C–C bond forming reactions shown in this study in a later section.

Oximes and oxime ethers

In 2012, Wertz and Studer reported a metal free TEMPO catalysed method for preparing oximes and oxime ethers from hydroxylamines and alkoxyamines (Fig. 20).¹⁰⁶

They utilised TEMPO, 4-OH-TEMPO or 4-acetamido-TEMPO (4-AcNH-TEMPO) for these reactions and while these all performed similarly, the 4-substituted radicals were more readily separated from the product compared to TEMPO. It was found that TEMPO (or the derivatives) could not act catalytically for aliphatic hydroxylamines, which were less reactive and in those cases an excess of TEMPO was required. For alkoxyamines and benzylic hydroxylamines it was possible to use catalytic amounts of the radical along with O₂ to produce products in good to excellent yields. They also showed that benzyl bromides could be converted to oxime ethers in a one-pot procedure where the alkoxyamines were formed *in situ*, although excess TEMPO (2.2 equivalents) was required in this case.

Suzuki *et al.* outlined a method for the aerobic oxidation of amines to oximes.¹⁰⁷ This is a rare example that does not utilise a nitroxyl radical as the stable radical. Here they have used 1,1-diphenyl-2-picrylhydrazyl (DPPH) in combination with a heterogeneous tungsten (WO₃/Al₂O₃) co-catalyst (Fig. 21).

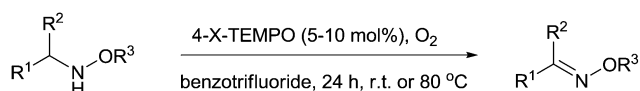


Fig. 20 TEMPO mediated oxidation of hydroxylamines and alkoxyamines to oximes and oxime ethers.

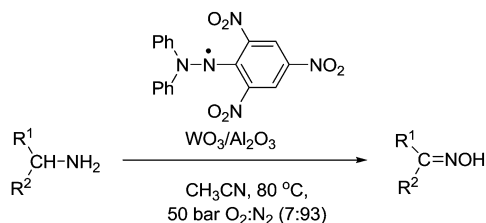


Fig. 21 Aerobic oxidation of amines to oximes using DPPH and WO₃/Al₂O₃.

The catalyst could oxidise alicyclic and aliphatic amines to their corresponding oximes in excellent yields. The catalyst showed good selectivity for amines. For substrates that possessed alcohol groups (*e.g.* 5-hydroxypentylamine and 4-hydroxycyclohexylamine) the amine could be oxidised and the alcohol group remained intact. They also demonstrated that the DPPH-WO₃/Al₂O₃ catalyst could be recycled and reused (3 cycles) without loss of performance. In the case of secondary amines, it was possible to oxidise these to their corresponding nitrones. In these studies, they used a pressurised reactor and a 7% O₂ gas mixture to ensure reactions were outside the flammability limits.

Synthesis of N-heterocycles

Nitrogen containing heterocycles are often the basis of natural products and pharmaceuticals, therefore efficient methods to produce such structures are valuable. Han and co-workers have published a number of papers describing the synthesis of N-heterocycles employing TEMPO and TEMPO derivatives as catalysts. In 2008, they reported that 4-methoxy-TEMPO could be utilised as a catalyst for the synthesis of 2-substituted benzoxazoles, benzothiazoles, and benzimidazoles utilising the route shown in Fig. 22.¹⁰⁸ They prepared a range of substituted heterocycles in fair to excellent yields.

In 2011, they described the synthesis of 2-aryl quinazolines by reacting arylmethanamines with either 2-aminobenzoketones or 2-aminobenzaldehydes (Fig. 23).¹⁰⁹ Once again this was a metal-free system but they employed 4-hydroxy-TEMPO as the catalyst in this instance. Products were obtained in good to excellent yields.

In 2012, they reported another method for the synthesis of 2-substituted quinazolines and 4*H*-3,1-benzoxazines and in this case, they utilised a catalyst system more similar to that employed for alcohol oxidation.¹¹⁰ Screening various conditions it was found that the addition of CuCl improved the yield and rate of these reactions. It was also noted that the addition of nitrogen ligands had a positive effect with 4-diazabicyclo[2.2.2]octane (DABCO) delivering the best performance, with optimised conditions shown in Fig. 24. The optimised conditions used lower loadings of 4-hydroxy-TEMPO and lower temperatures compared to their previous study. A range of substituted heterocycles were prepared in good to excellent yields for the majority of cases.

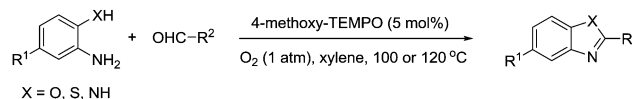


Fig. 22 Synthesis of benzoxazoles, benzothiazoles, and benzimidazoles using 4-methoxy-TEMPO.

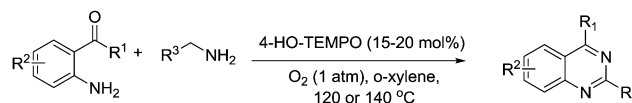


Fig. 23 Synthesis of 2-aryl quinazolines using 4-HO-TEMPO.



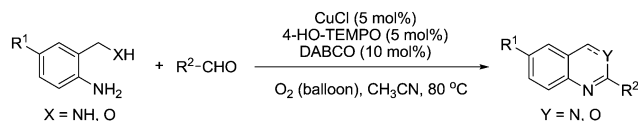


Fig. 24 Synthesis of 2-substituted quinazolines and 4H-3,1-benzoxazines using Cu/4-HO-TEMPO.

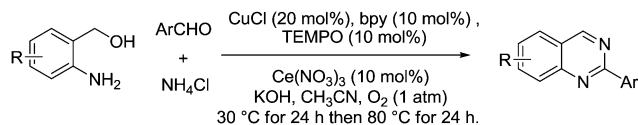


Fig. 25 Synthesis of quinazoline derivatives from (2-aminophenyl)methanols, aldehydes and ammonium chloride.

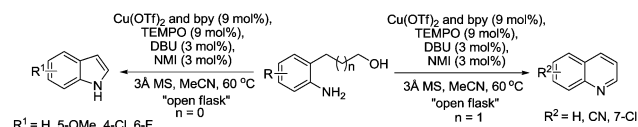


Fig. 26 Synthesis of N-heterocycles *via* Cu/TEMPO catalysed aerobic oxidation of amino alcohols.

In 2013, Chen *et al.* developed a three-component cascade synthesis of quinazoline derivatives using CuCl, bpy and TEMPO in the presence of cerium nitrate (Fig. 25).¹¹¹ (2-Aminophenyl)-methanols and a variety of substituted benzaldehydes were converted smoothly to their corresponding 2-arylquinazolines in moderate to excellent yields.

In 2012, we reported a method for synthesising indoles and quinolines *via* aerobic oxidation of amino alcohols.¹¹² As shown in Fig. 26, we utilised the Cu/TEMPO catalyst system previously optimised by Kumpulainen and Koskinen.²⁹

This study differs from the previous examples by Han and co-workers because in this case, alcohol oxidation is a key step in the reaction. Once the aldehyde is formed an intra-molecular cyclisation and dehydration takes place to form the heterocycle. Indoles were prepared in moderate to good yields, although it was found that extended reaction times led to poorer yields and control experiments indicated that the catalyst caused product decomposition. The selectivity of Cu/TEMPO for primary alcohols was demonstrated using a substrate containing a secondary alcohol group, which remained intact. For the synthesis of quinolones it was found that 1,2,3,4-tetrahydroquinoline-2-one was formed as by-product, indicating that upon cyclisation there were two competing pathways; dehydration or further alcohol oxidation to give 1,2,3,4-tetrahydroquinoline-2-one. The use of molecular sieves and a drying tube helped promote the synthesis of the desired quinoline.

In 2013, Li and co-workers developed a room temperature oxidative aromatisation of substituted Hantzsch 1,4-dihydropyridines (1,4-DHPs) using either FeCl₃ or CuCl₂ combined with NaNO₂ and TEMPO (Fig. 27).¹¹³ In most cases, FeCl₃ was used although there were some examples where CuCl₂ gave better performance. It was possible to obtain a range of products in excellent yields in under 60 min.

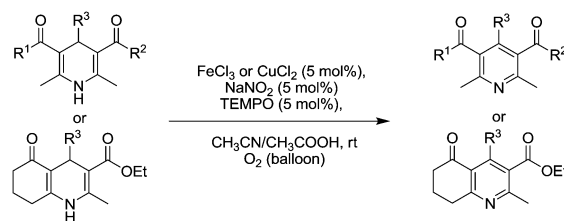


Fig. 27 oxidative aromatisation of substituted Hantzsch 1,4-dihydropyridines (1,4-DHPs).

Whilst this review focuses on the use of stable radicals as catalysts, it is worth mentioning related work in the synthesis of heterocycles. Mancheño and co-workers have utilised TEMPO derived oxoammonium salts as a stoichiometric oxidant for the synthesis of oxazinones,¹¹⁴ and substituted quinolines and dihydroquinazolines.^{115,116} While Chiba and co-workers reported the synthesis of substituted isoxazoles and pyrazoles, *via* TEMPO mediated C–H bond oxidation of oximes and hydrazones, although excess quantities of TEMPO (3–6 equiv.) were employed in this example.¹¹⁷

C≡N bond formation

Very recently, there were four independent reports (including one from our group), published within a short space of time, demonstrating the use of aerobic Cu/nitroxyl systems for the synthesis of nitriles.^{118–121} The nitrile group is an important functionality in chemistry and often the synthesis of nitriles relies on undesirable methods. In 1983, Semmelhack and Schmid reported that TEMPO could be employed for the electro-oxidation of amines to nitriles;¹²² however there were no aerobic methods for selectively producing nitriles using such radicals. In these recent publications, three papers focused on the synthesis of nitriles from alcohols or aldehydes using aqueous ammonia as the nitrogen source (Fig. 28). Starting from alcohols, the catalyst produces the aldehyde and subsequently oxidises the imine, which readily forms *via* the aldehyde and ammonia.

Tao and co-workers used 5 mol% Cu(NO₃)₂ (no ligand was used), 5 mol% TEMPO, 3 equivalents of NH₃ and DMSO as the solvent. The flask was flushed with O₂ and then sealed and heated to 80 °C for 5 hours. For aldehydes the reaction could be performed without TEMPO. A range of benzylic substrates were demonstrated but the catalyst was not suitable for aliphatic substrates. They also demonstrated that a one-pot procedure could be employed for the synthesis of aryl amides from the corresponding benzyl alcohol. Once the nitrile had been

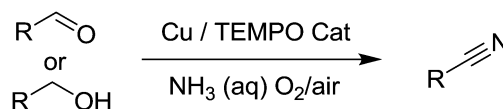


Fig. 28 Synthesis of nitriles from alcohols or aldehydes using Cu/TEMPO/O₂ systems.



produced, acetaldoxime and water were then added to the reaction mixture and heated to 100 °C for 24 hours.

Huang and co-workers described a method that utilised a more reactive Cu(I) system. This enabled a wide range of functionalised alcohols (including aliphatic) to be converted to the corresponding nitrile, in good to excellent yields, under mild conditions. They utilised a catalyst system composed of 5 mol% CuI, 5 mol% bpy and 5 mol% TEMPO. They added 2 equivalents of aqueous ammonia and carried out the reaction under an O₂ atmosphere (balloon). Activated alcohols were converted at room temperature (24 hours) with ethanol as the solvent. Reactions with aliphatic substrates were carried out in acetonitrile at 50 °C (24 hours). In the case of benzylic alcohols they also demonstrated that a one-pot procedure could be employed for the synthesis of biaryl heterocycles. Once the nitrile was produced reagents were then added to convert the nitrile to tetrazoles, imidazolines, thiazolidines, triazolopyridines and oxazolines.

We avoided the use of pure O₂ atmospheres and developed methods that used air (open flask) or dilute oxygen (8%) mixtures. Activated aldehydes were converted to the corresponding nitrile using an "open flask" method. 10 mol% Cu(OTf)₂, bpy and TEMPO were used. The water soluble radical 4-sulfonatoxy-TEMPO was also used as this could be readily washed out from the product. The reaction was carried out in acetonitrile–water and NaOH, with the presence of this base improving the reaction rate. This system was open to the air and therefore aqueous ammonia was slowly added during the reaction to replace ammonia that had evaporated. The "open flask" method could be used from 25–70 °C, above this temperature the ammonia evaporated before reacting. It was found that aliphatic substrates were slow to react using this method, therefore based on Stahl's Cu(I) studies,³⁰ we switched to using [Cu(MeCN)₄][OTf]. The improved reactivity of Cu(I)/TEMPO is not maintained when substantial amounts of water are present, therefore acetonitrile was used along with 2.5 equivalents ammonia. To prevent evaporation of ammonia, a balloon containing air was attached to the condenser. The modified method allowed octanal to be converted cleanly at 25 °C while 1-octanol required 50 °C. With an aromatic aldehyde at a temperature of 120 °C, inexpensive CuCl₂ could be used at 1 mol% along with 1 mol% 4-sulfonatoxy-TEMPO. At such a temperature, a pressurised reactor is required to prevent ammonia evaporation; therefore a pressurised atmosphere of 8% O₂ was used.

Kim and Stahl had also found that nitriles could be produced from alcohols and ammonia; however due to the aforementioned studies they focused on the selective oxidation of primary amines to nitriles. Oxidation of amines can lead to a variety of products,¹²³ and as discussed earlier Cu/TEMPO catalyst systems can catalyse the aerobic oxidation of primary amines to the corresponding homocoupled imines. In those studies nitriles are sometimes seen as a by-product.^{102,103} Kim and Stahl demonstrated that unhindered radicals ABNO and AZADO improved the yield and selectivity of nitrile *versus* homocoupled imine. As shown in Fig. 29 the optimised

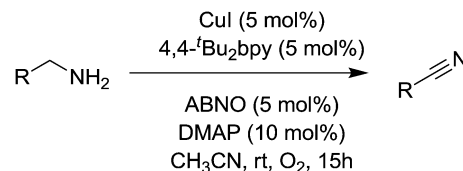


Fig. 29 Aerobic oxidation of primary amines to nitriles.

conditions utilised 4,4'-*t*Bu₂bpy (4,4'-di-*tert*-butyl-2,2'-bipyridyl) as a ligand, DMAP (4-dimethylaminopyridine) as the base and ABNO as the radical.

This catalyst system was able to convert a range of benzylic, allylic and aliphatic primary amines to nitriles, in good to excellent yields. Preliminary mechanistic experiments indicate that the nitrile is not formed *via* the homocoupled imine, but rather that catalyst carries out a double oxidation; oxidation of the amine to the primary imine followed by oxidation of this imine to the nitrile.

Carbon–carbon bond formation

The formation of C–C bonds is a powerful tool in organic synthesis. Recently, there have been several reports that have utilised stable radicals for the construction of C–C bonds, using a number of different approaches.

In 2008, Studer and co-workers reported the use of TEMPO as an aerobic catalyst for the homocoupling reaction of aryl-, alkenyl- and alkynyl-Grignard reagents.¹²⁴ More recently, they followed this up with a study showing that TEMPO could be used as a catalyst for the cross-coupling reaction between nitrones and alkynyl-Grignard reagents (Fig. 30).¹²⁵

This is a useful transformation because the alkynylated nitron products are valuable precursors for biologically useful isoxazoles. The authors also demonstrated that they could prepare a range of isoxazoles in good yields, using these products.

In 2012, Jiao and co-workers described the use of TEMPO to catalyse the C–C bond formation between two Csp³–H bonds.¹²⁶ This transformation provided a simple and efficient approach to modify 9,10-dihydroacridine derivatives at the 9-position under the conditions shown in Fig. 31.

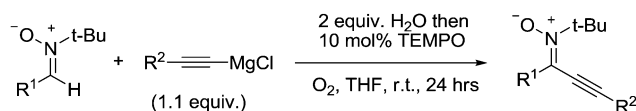


Fig. 30 TEMPO mediated cross-coupling reaction between nitrones and alkynyl-Grignard reagents.

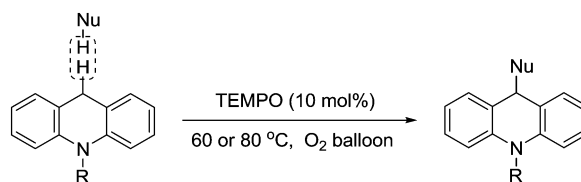
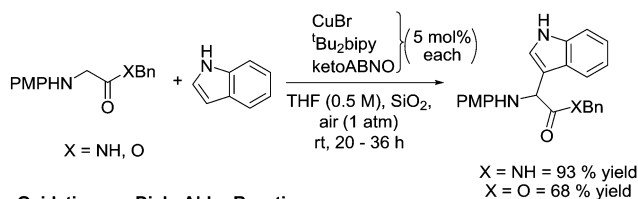


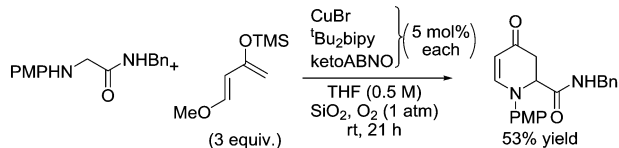
Fig. 31 TEMPO-catalysed aerobic oxidative C–C coupling of 9,10-dihydroacridines with carbon nucleophiles.



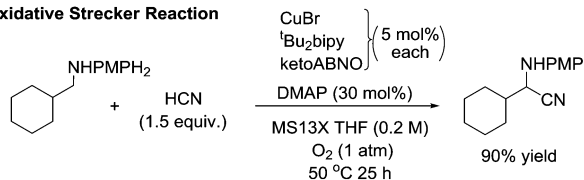
Oxidative Friedel-Crafts (CDC) Reactions



Oxidative aza-Diels-Alder Reaction



Oxidative Strecker Reaction

Fig. 32 Examples of oxidative reactions of amines using Cu/ketoABNO/O₂.

They demonstrated this for acridines with a range of aliphatic and aromatic groups attached to the nitrogen and a number of different nucleophiles (examples include nitroethane, nitromethane, malonate and malononitrile).

As discussed earlier, Sonobe *et al.* utilised a Cu/ketoABNO system for the synthesis of imines from amines.¹⁰⁵ In this study they also demonstrated a number of C–C bond forming reactions, by reacting the formed imines. They carried out the nucleophilic addition of a Grignard reagent to an imine that had been produced *via* oxidation catalysis. They also carried out a series of coupling reactions, with some example shown in Fig. 32.

As well as the reactions shown in Fig. 32, they also demonstrated that an asymmetric aerobic CDC reaction could be carried out between a glycine ester and a nitroalkane. There are very few examples of aerobic asymmetric CDC reactions and in this case the copper was ligated with a chiral bis(oxazoline) ligand. This impressive study demonstrates how these oxidation catalysts have the potential to be very valuable tools in organic synthesis.

Indole derivatives are known to exhibit biological activity and are common features of natural products. Liu and co-workers demonstrated that TEMPO could be used as a catalyst for the trimerisation of indoles toward 2,2-disubstituted indolin-3-one derivatives in moderate to excellent yields (Fig. 33).¹²⁷ In their first study, they utilised TEMPO without any metal co-catalysts, and subsequently they also used CuCl. The use of CuCl enabled the loading of TEMPO to be reduced and in some cases the reaction time was also reduced. The Cu/TEMPO system also delivered better performance for derivatives containing strong electron-withdrawing groups. In the system utilising only TEMPO, when $\text{R} = \text{NO}_2$ or CN , the desired product was not obtained, while the Cu/TEMPO system afforded these products in moderate yields. They also showed that the Cu/TEMPO system could be used for the dimeric reaction of 2-substituted indoles.

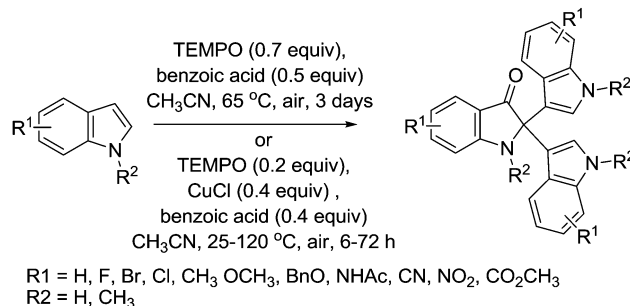


Fig. 33 Trimeric reaction of indoles using TEMPO.

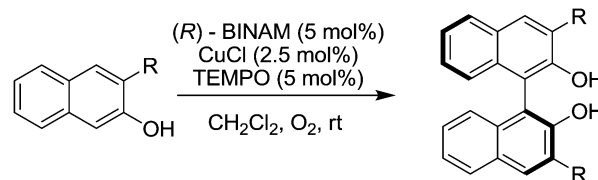


Fig. 34 Oxidative coupling of 2-naphthol derivatives.

Sekar and co-workers reported that TEMPO improved the catalytic performance of copper catalysed enantioselective coupling of 2-naphthol derivatives (Fig. 34).¹²⁸ In this study it was found that the reaction could proceed with just the (*R*)-BINAM-CuCl catalyst (where BINAM = 1,1'-binaphthyl-2,2'-diamine), but the addition of TEMPO significantly improved the reactivity, enabling these reactions to be carried out at room temperature (rather than 90 °C) in shorter reaction times (2–4 days rather than 7–9 days). A range of 1,1'-binaphthol derivatives were prepared in good to excellent yields (77–98%) with enantioselectivities up to 97% ee (depending on the substituents).

There are also some recent examples using tris(4-bromophenyl)aminium hexachloroantimonate (TBPA⁺ SbCl₆[−]). This radical cation (Fig. 35) has been used as an aerobic oxidation catalyst in C–C bond forming reactions.

Jia *et al.* prepared substituted quinolines from peptides and glycine derivatives using this radical cation.¹²⁹ Optimisation studies found that in most cases, using InCl₃ as a co-catalyst resulted in improved yields and a range of substituted quinolines were prepared with the majority in good yields (Fig. 36).

It was found that O₂ was vital for the reaction to take place and the authors proposed some mechanistic details. They believe that it is likely O₂ first reacts with TBPA⁺, forming a peroxy radical cation species. This peroxy species is then responsible for initiating the reaction by abstracting a

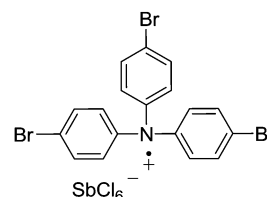


Fig. 35 Tris(4-bromophenyl)aminium hexachloroantimonate.



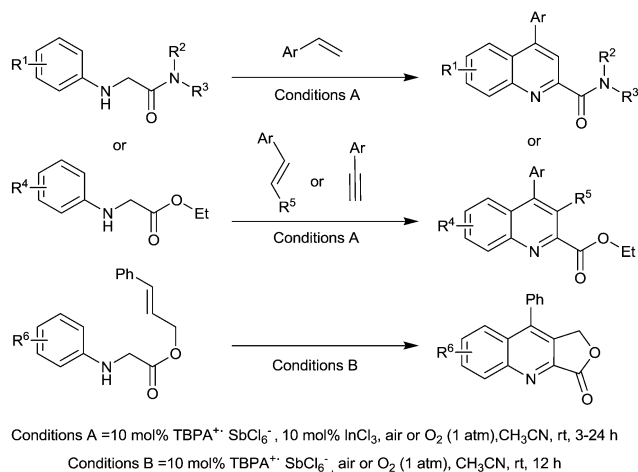


Fig. 36 Aerobic synthesis of quinolines using TBPA⁺• SbCl₆⁻.

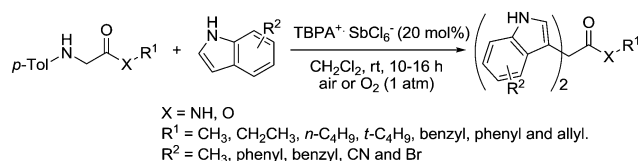


Fig. 37 Friedel–Crafts reaction using TBPA⁺• SbCl₆⁻.

hydrogen atom from the substrate (on the aliphatic carbon adjacent to the nitrogen).

It was shown that TBPA⁺• SbCl₆⁻ could be used to catalyse a double Friedel–Crafts reaction of glycine derivatives with indoles (Fig. 37).¹³⁰ A range of bisindolylmethane derivatives were prepared in good to excellent yields.

The importance of C–C bond formation means that this is likely to be an area that will continue to grow and develop. Further information in this area has been highlighted in a recent review by Mancheño and Stopka which also includes closely related systems not under the remit of this review, for example, non-aerobic systems and the use of oxoammonium salts as stoichiometric oxidants.¹³¹

Miscellaneous reactions

In 2011, Yang and co-workers described the use of TEMPO as a catalyst for oxidative S–S bond formation.¹³² In this example, 2,2'-disubstituted benzothiazole disulphide is used in the production of rubber, however S–S bond formation is generally a useful transformation. It was shown this product could be prepared catalytically using 5 mol% TEMPO (Fig. 38).

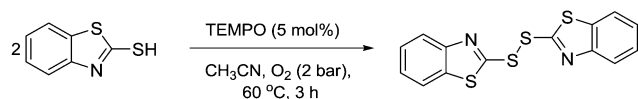


Fig. 38 Aerobic oxidative homocoupling of 2-mercap-tobenzothiazole catalysed by TEMPO.

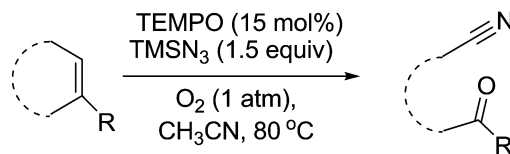


Fig. 39 TEMPO mediated cleavage, oxygenation and nitrogeneration of C=C double bonds to form oxo nitriles.

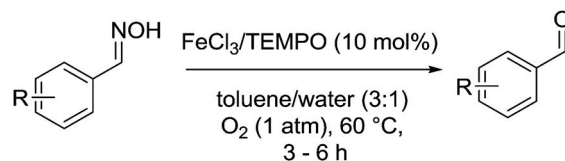


Fig. 40 Oxidative deprotection of aldoximes.

Wang and Jiao discovered that TEMPO could be used as a catalyst for the synthesis of useful oxo nitrile compounds.¹³³ These molecules can be used as precursors for the synthesis of desirable chemicals such as isoquinolines, α -hydroxyketones and alkenenitriles. The TEMPO mediated reaction is outlined in Fig. 39 and involves the cleavage, oxygenation and nitrogeneration of a C=C double bond. The protocol uses TEMPO as the catalyst and requires the use of trimethylsilyl azide (TMSN₃). In the case of benzocycloalkenes, the reaction demonstrated good regioselectivity with oxygenation occurring at the benzylic site. In the case of aliphatic alkenes, the reaction was slower and it was found that the addition of phenyliododiacetate improved the yield. They also looked at terminal alkenes in the form of styrenes, which results in the formation of the corresponding carbonyl compound.

Ding, Cao and co-workers have described the oxidative deprotection of aldoximes using an FeCl₃/TEMPO system (Fig. 40).¹³⁴ They postulate that cleavage of the oxime produces NO, which then becomes an active species in the catalytic cycle and improves catalytic performance. A number of aldoximes were oxidised to their corresponding aldehydes in excellent isolated yields, however ketoximes were slow to react and resulted in low yields.

Conclusions and outlook

In recent years there have been important strides made in the use of stable radicals for aerobic oxidation catalysis. Alcohol oxidation has gained a lot of research interest and there are now a variety of different methods that can be used efficiently for both primary and secondary alcohols. Importantly, these methods are tolerant of many functionalities and this means that the potential substrate scope is extremely wide. The performance of these systems is arguably at the stage where they could be utilised on a larger industrial scale for the synthesis of some products. There have also been a growing number of reports in which stable radicals are shown to have potential for a wider range of oxidation reactions. In some



cases, the performance (e.g. catalyst loading/yields) may not yet be practical, but this is something that should improve as the area matures. We believe that the variety of possible reactions will continue to increase. This may well be driven by a move towards more reactive and sterically diverse radicals. The recent application of radicals such as ABNO and AZADO has already demonstrated that they can have significant advantages over the commonly used TEMPO. The level of sophistication of stable radicals may also increase as it is becoming clear that we can improve the performance of catalysts by tuning both the sterics and electronics of these radicals.^{76,135,136} As we have highlighted, there are also a few examples where radicals other than nitroxyls have been exploited, and again utilising a wider range of stable radicals may lead to a greater diversity of potential reactions. We believe we are entering an exciting time for this area of chemistry and the prospects for oxidation catalysis with stable radicals are extremely promising.

Ultimately the sign of success for a catalytic method is that it is used on a larger, industrial scale. However, we believe there remain a few challenges to such aerobic systems being employed on a larger scale. From a catalyst performance/cost perspective, if these catalysts are to be used for producing less expensive fine chemicals (e.g. fragrance and flavour molecules), then the radicals will need to be recovered and re-used for a process to be economically viable. The cost of radicals such as TEMPO is something that has been previously discussed in relation to industrial applications,⁵ with the use of solid supported TEMPO highlighted as a way of improving the practicality on a larger scale. Unhindered radicals (e.g. AZADO and ABNO), have emerged as very promising catalysts and these radicals are likely to be more expensive than TEMPO. Consequently, the recovery and re-use of such radicals will be key for some applications.

Another significant obstacle hindering the industrial viability of these catalytic systems is the use of O₂ as the terminal oxidant. Although oxygen is utilised on a large scale for the production of commodity chemicals (e.g. terephthalic acid) it is rarely used by the pharmaceutical industry. In a review of large-scale oxidations in the pharmaceutical industry (written by researchers from Pfizer), they stated: "Oxygen gas has the advantage of being the least expensive and most readily available oxidant, but the safety issues surrounding its use make it one of the least frequently used reagents".¹³⁷ As mentioned earlier, the majority of industrial applications for TEMPO utilise bleach as the oxidant.⁵ More recently Holan and Jahn reported the use of TEMPO and AZADO for the oxidation of alcohols.¹³⁸ In this case, they utilised *t*-BuONO as a stoichiometric oxidant under anaerobic conditions. The authors point out that such an approach avoids the hazards associated with using O₂. In our own opinion, such an approach is probably a more attractive option to those working in the pharmaceutical industry at the present time. But using *t*-BuONO as a stoichiometric oxidant is most likely not a viable option for the production of cheaper fine chemicals and in these cases aerobic methods would be more desirable.

For aerobic oxidations to be exploited on a larger scale, an important task is demonstrating the use of safer methods for

aerobic oxidations. As is evident in this review, it is common in academic studies that pure O₂ atmospheres are utilised. On a small scale, the dangers of O₂ may be limited but on a larger scale, even air would be too dangerous to use with organic solvents. Utilising air may be viable for aqueous systems (e.g. laccase/nitroxyl systems) but processes using organic solvents reactions require *limiting oxygen concentrations* (LOC). The LOC is the concentration of oxidant below which combustion is not possible under specified conditions. For most organic solvents (and substrates) an O₂ concentration of less than 10% is usually needed to achieve LOC.¹³⁹ A downside of using dilute O₂:N₂ gas mixture is that reactions require comparatively higher pressures (e.g. tens of bars) to achieve sufficient O₂ concentrations in the liquid phase. Such pressures are another deterrent to those in the pharmaceutical industry. It seems clear that the best way to make such pressurised systems scalable is to use a continuous flow system and as we have highlighted there are already some examples of flow systems with stable radicals. Continuous flow is a standard way of improving the efficiency of a process, but an important aspect of this mode of operation is that it allows much smaller reactors to be used, making the dangers of pressurised systems much easier to handle. The use of microreactors and continuous flow is another area that holds promise as a method of scaling up oxidation reactions. In the case of microreactors it is known that it is possible to work under conditions that would not be suitable using conventional reactor systems; of relevance here is the ability to use pure O₂ and work inside the explosive regime without adverse outcomes.^{140,141} We believe that such approaches to reaction engineering will help aerobic systems become more practical on a larger scale.

Acknowledgements

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Homogeneous Catalysis

Synthesis of 2-Alkynoates by Palladium(II)-Catalyzed Oxidative Carbonylation of Terminal Alkynes and Alcohols

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Abstract: A homogeneous Pd^{II} catalyst, utilizing a simple and inexpensive amine ligand (TMEDA), allows 2-alkynoates to be prepared in high yields by an oxidative carbonylation of terminal alkynes and alcohols. The catalyst system overcomes many of the limitations of previous palladium carbonylation catalysts. It has an increased substrate scope, avoids large excesses of alcohol substrate and uses a desirable solvent. The catalyst employs oxygen as the terminal oxidant and can be operated under safer gas mixtures.

2-Alkynoates (alkynoate esters) are incredibly valuable building blocks for organic synthesis as they can be transformed into a diverse range of other desirable products.^[1] Unfortunately the synthesis of 2-alkynoates often has several drawbacks, with only a limited number of synthetic methods for preparing these esters. For example, lithiated alkynes can be treated with an alkyl chloroformate,^[2,3] and alkynyl carboxylic acids can be esterified using carbodiimide coupling reagents such as DCC^[4] and EDCI (Figure 1).^[5] Such methods utilize stoichiometric reagents and also have substrate limitations. 2-Alkynoates can also be prepared catalytically with alkynes, CO₂, and alkyl halides.^[6] Whilst the use of CO₂ is desirable, employing alkyl halides can have disadvantages and there has been a limited substrate scope demonstrated to-date using this route. An alternative is to carry out a catalytic oxidative carbonylation of terminal alkynes and alcohols. Replacing alkyl halides with alcohols is preferable, as a wide range of alcohols are commercially available and are normally inexpensive. Carbon monoxide is a widely available, sustainable, and inexpensive carbonyl source. Palladium catalyzed carbonylations are well established, however oxidative carbonylations have been less developed to-date.^[7] This underdevelopment is apparent in the case of 2-alkynoates. The oxidative carbonylation of alkynes with al-

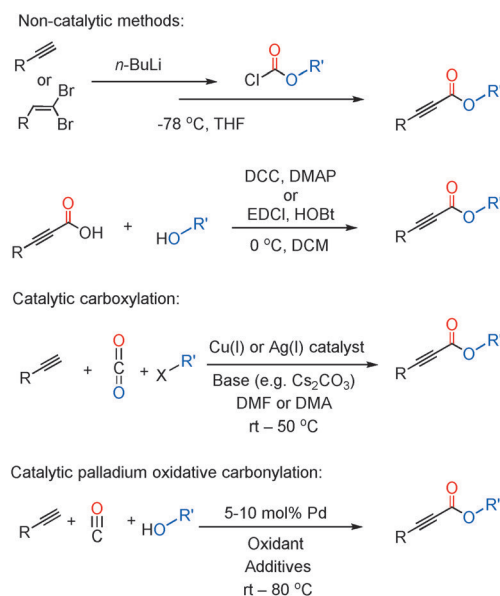


Figure 1. Examples of methods for the preparation of 2-alkynoates.

cohols using Pd^{II} catalysts dates back some time, however, reactions do not always produce 2-alkynoates and in some cases dicarbonylation is prevalent and a range of products can be produced.^[8] In terms of catalyst systems that can prepare 2-alkynoates, there have only been a few reports using homogeneous Pd^{II} catalysts,^[9–13] and there are some significant limitations. In these examples, the catalyst loadings are high and there is only one example of O₂ being used to directly reoxidize the catalyst.^[13] The use of only a limited number of substrates has been demonstrated so far and simple alcohols (such as methanol) have been the main focus. Furthermore, the alcohol is generally used as the solvent and when this is not the case it is used in very large excess.

More recently, an aerobic system which used a heterogeneous palladium catalyst (Pd on carbon) was reported.^[14] High yields of the desired 2-alkynoate could be produced when 1,4-dioxane was used as the solvent (THF was the next best solvent). A number of alkynes were shown to be suitable, but only primary alcohols acted as suitable nucleophiles. An attractive feature of this system is the ability to recycle the catalyst, however the inability to oxidize secondary alcohols and the use of 1,4-dioxane as the solvent are significant drawbacks.

Our aim was to try and address the limitations of previous catalyst systems and develop a more efficient and widely applicable method. We are interested in exploiting ligands to improve the performance of Pd^{II}-catalyzed oxidation reactions,

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and developing systems which use sustainable oxidants such as O_2 and H_2O_2 .^[15] Ligand modulation has been successfully developed for other Pd^{II} -catalyzed reactions,^[16] but as Beller and co-workers highlighted in their recent review,^[7c] this is an area that needs to be addressed in the field of oxidative carbonylations. Another aim was to demonstrate that these aerobic systems could be operated under safer oxygen concentrations and with a safer solvent.

We screened a wide variety of ligands and other reaction conditions and a comprehensive summary of these details can be found in the Supporting Information. It was found that adding tetrabutylammonium iodide (TBAI), an additive previously employed in these reactions,^[14] was essential for good performance. In terms of solvents, we were pleased to find that ethyl acetate was the best solvent for these reactions. Ethyl acetate is a solvent which is a "recommended" choice by pharmaceutical companies,^[17] unlike solvents such as DMF or 1,4-dioxane and THF, which have previously been used for these reactions. DMF and 1,4-dioxane are classed as hazardous and are to be avoided, while THF is "problematic".^[17] Furthermore, aerobic reactions in ethereal solvents such as 1,4-dioxane and THF are particularly dangerous due to their propensity to form potentially explosive peroxides. It is possible that peroxide formation in 1,4-dioxane plays a role in the catalysis, as this solvent has not only been used for oxidative synthesis of 2-alkynoates, but it has also been the solvent of choice for oxidative aminocarbonylations to synthesize 2-ynamides.^[18] There are examples of other palladium oxidation catalysts, in which in situ formation of peroxides in THF^[19] or 1,4-dioxane^[20] are responsible for the reactivity. One would assume that the dangers of peroxide-forming solvents would severely limit the use of these catalyst systems on a larger scale.

Additionally, we screened a range of ligands, which had a significant effect on the substrate conversion and selectivity to the desired 2-alkynoates. Table 1 shows a few examples and further details are in the Supporting Information.

To-date the only example of a Pd^{II} catalyst that directly uses O_2 , is based on PPh_3 as a ligand.^[13] However, phosphine ligands

are not ideal candidates for oxidation reactions and it can be seen from our screening studies that other ligands delivered superior performances. The best overall performance in terms of rate and selectivity was obtained with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (Entry 6 in Table 1). After optimization, we found that a ratio of 10:1 TMEDA/ Pd was optimal. The performance of TMEDA was very pleasing due to the fact that this is a readily available and very inexpensive amine ligand. Interestingly, the ethylene spacer in TMEDA was very important and having a methylene (TMDAM), propylene (TMPDA), or butylene (TMBDA) spacer did not result in high selectivity to the desired product.

We utilized $Pd(OAc)_2$ as the palladium source and as shown in Table 2, found that the counter ion was very important. Successful catalysis was only obtained with alkyl carboxylate anions and there are a few possible reasons for this. Acetate (and similar carboxylate anions) are known to play a key role in C-H activation reactions,^[21] and acetate effects have also been shown for the Pd^{II} -catalyzed hydration and dimerization reactions of terminal alkynes.^[22] Although some of the homogeneous systems that were previously reported used $PdCl_2$ and $PdBr_2$ salts, these methods also added NaOAc to the reaction.^[9,10] However, when alcohols are replaced with amines in these oxidative carbonylation reactions to produce 2-ynamides, there is not a need for a source of acetate.^[18] Therefore it is possible that the need for a carboxylate anion is related to its ability to deprotonate the Pd^{II} -coordinated alcohol. In previous studies on aerobic Pd^{II} -catalyzed oxidations of alcohols, it was found that acetate is often key in this regard.^[23]

In terms of gas compositions, we can manage the dangers of using pressurized O_2 or air on a small scale in our laboratory, and although we used such gas mixtures in our optimization experiments (see the Supporting Information), we wanted to demonstrate that the reactions could be carried out under safer conditions. Carbon monoxide is a flammable gas and pure CO/O_2 mixtures are within the explosion limits as the

Table 1. Some examples of the ligand effects on the yield of respective 2-alkynoates.

Entry	Ligand	Amount [mol %]	Yield [%] ^[a]
1	–	–	10
2	PPh_3	2	20
3	Phen	1	32
4	NEt_3	20	19
5	TMDAM	10	12
6	TMEDA	10	73
7	TMPDA	10	18
8	TMBDA	10	11

[a] The yields were determined by GC using an internal standard. Experiment details and further examples of optimizations can be found in the Supporting Information.

Table 2. Influence of different Pd^{II} salts on the catalytic performance.

Counterion X	Conv. alkyne [%] ^[a]	Conv. alcohol [%] ^[a]	Yield [%] ^[a]
I^-	6	0	0
Cl^-	12	0	0
$F_3C-C(=O)O^-$	27	5	0
$CH_3-C(=O)O^-$	92	89	82
$(CH_3)_2C-C(=O)O^-$	90	87	84
$CH_3CH_2-C(=O)O^-$	80	89	74

[a] Conversions and yields were determined by GC using an internal standard.

lower flammability limit (LFL) of carbon monoxide in air is 11.5 vol% at 100 °C.^[24] Additionally, we also need to take into account that we are using organic solvents and those have their own flammability limits, so it is important to try and use limiting oxygen concentrations (LOC) when using batch conditions. The LOC of ethyl acetate at 100 °C is 9.4 vol% O₂ at a pressure of 1 bar and 9.9 vol% O₂ at a pressure of 20 bar.^[25] Therefore we carried out our substrate-scope studies using 5 bar of CO with 35 bar of an O₂/N₂ gas mixture (8:92). By using an O₂/N₂ gas mixture we should not only be below the LOC of the solvent but also the LFL of CO. A lower catalyst loading could be employed with 35 bar of air (see the Supporting Information for details), but we wanted to demonstrate the use of a gas mixture that should be safe with regards to the solvent and CO.

With optimized conditions in hand, we demonstrated that we could produce a significant number of 2-alkynoates (1–33), many of which in excellent yields. We examined a number of different primary alcohols using phenylacetylene as the alkyne (Figure 2) and a number of alkynes using benzyl alcohol as the nucleophile (Figure 3). In previous reports, a large excess of alcohol is normally required, but in the case of primary alcohols we could employ equimolar quantities of alkyne and alcohol. As shown in Figure 2, we could utilize both activated and unactivated alcohols. Substrates with electron-withdrawing or -donating substituents proceeded readily. Heteroatoms were tolerated, although a lower yield was obtained with a pyridine-containing substrate (11). Benzyl alcohols bearing chloro and

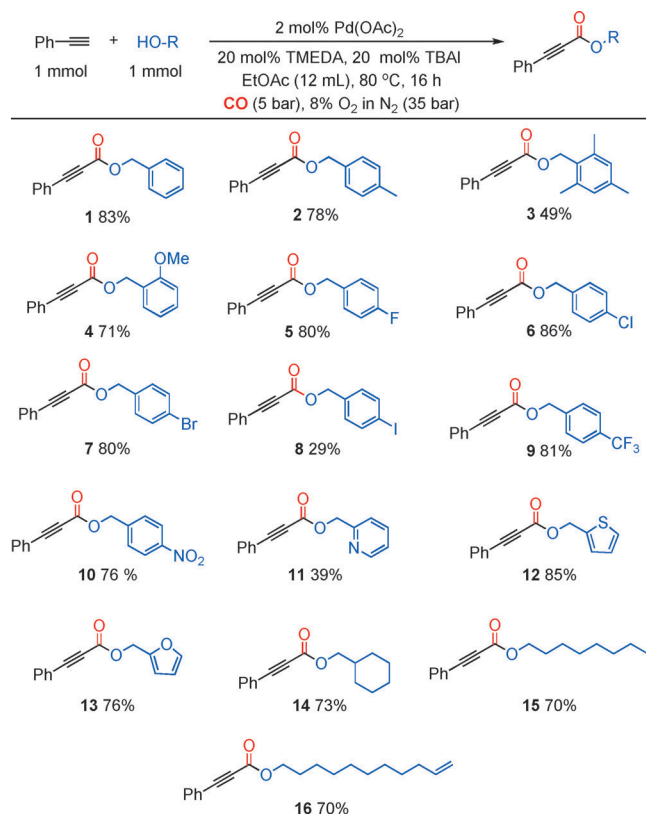


Figure 2. Synthesis of 2-alkynoates with various primary alcohols.

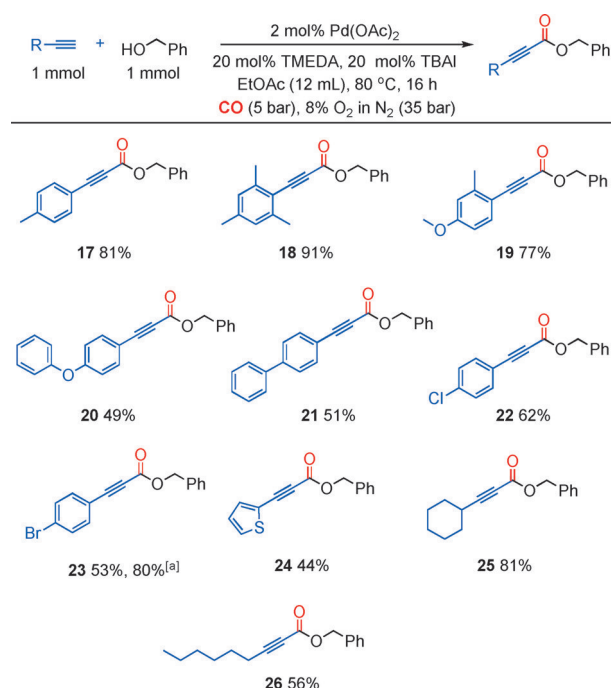


Figure 3. Synthesis of 2-alkynoates with various alkynes. [a] 2 mmol benzyl alcohol.

bromo substituents (6 and 7) worked well, as did an aliphatic substrate bearing a terminal olefin (16). Such products have potential to be further functionalized at a later stage. Interestingly, the same substituents had a differing effect on the alkyne and the alcohol. For examples, compare 3 to 18 and 7 to 23.

Secondary alcohols are more challenging substrates, which is demonstrated by the fact that there are just a few examples in the literature that are restricted to simple substrates such as 2-propanol. We found that we could utilize secondary alcohols with only a slight change to our method, employing a slightly higher catalyst loading (3 mol% Pd(OAc)₂) and two equivalents of the alcohol (Figure 4). In the case of chiral alcohols, we demonstrated that the corresponding alkynoates could be produced with the chirality maintained. Previously, chiral 2-alkynoates have been used for Pauson–Khand reactions.^[4] In this case, the 2-alkynoates were prepared by more traditional methods using alkynyl carboxylic acid derivatives, and in a number of cases these methods were unable to produce the desired 2-alkynoate.

In conclusion, our study has made significant strides towards developing efficient and scalable oxidative carbonylation methods for the synthesis of 2-alkynoates. By studying a wide range of variables it has become clear that these reactions are complex and a number of factors greatly influence their performance. This highlights the need for a greater mechanistic understanding of Pd^{II}-catalyzed oxidative carbonylation reactions; something which is currently lacking in this area. We have demonstrated that ligands can have a profound effect on these reactions and pleasingly TMEDA, a very inexpensive amine, was found to deliver an excellent performance. The catalyst has a wider/more diverse substrate scope than previous

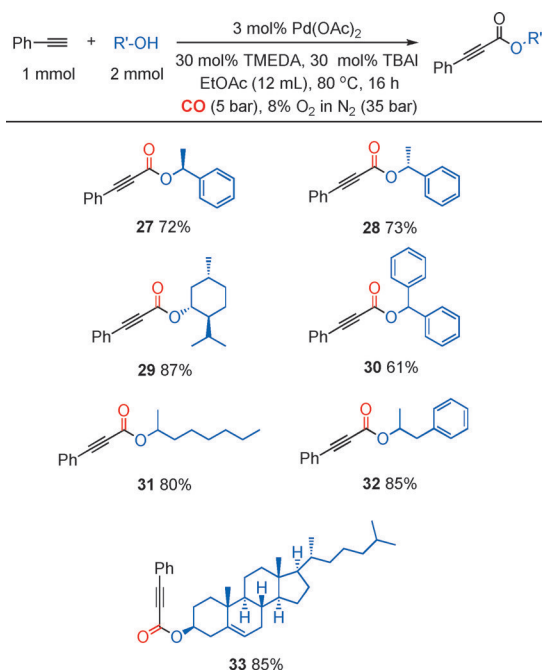


Figure 4. Synthesis of 2-alkynoates with secondary alcohols.

examples and can utilize O_2 to directly reoxidize the catalyst. The system utilizes ethyl acetate, an industrially preferred solvent, and does not require large excess of the alcohol substrates. The work also highlights the importance of using safer gas mixtures to avoid potentially explosive conditions. Further work will examine if we can improve the performance of a wider range of oxidative carbonylation reactions.

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Keywords: alkynes • carbonylation • homogeneous catalysis • oxidation • palladium

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Palladium(II)-Catalysed Aminocarbonylation of Terminal Alkynes for the Synthesis of 2-Ynamides: Addressing the Challenges of Solvents and Gas Mixtures

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2-Ynamides can be synthesised through Pd^{II} catalysed oxidative carbonylation, utilising low catalyst loadings. A variety of alkynes and amines can be used to afford 2-ynamides in high yields, whilst overcoming the drawbacks associated with previous oxidative methods, which rely on dangerous solvents and gas mixtures. The use of [NBu₄]I allows the utilisation of the industrially recommended solvent ethyl acetate. O₂ can be used as the terminal oxidant, and the catalyst can operate under safer conditions with low O₂ concentrations.

2-Ynamides are valuable building blocks in the synthesis of heterocycles^[1] and biologically active molecules.^[2] There are a number of methods for the preparation of 2-ynamides. Examples of non-catalytic approaches include the coupling of alkynyl carboxylic acids with amines, using *N*-hydroxysuccinimide and the coupling reagent *N,N'*-dicyclohexylcarbodiimide (DCC) in 1,4-dioxane.^[1b] Terminal alkynes, amines and CO were utilised to prepare 2-ynamides by Hoberg and Riegel; however, they employed Ni^{II} complexes as a stoichiometric reagent.^[3] Ideally, 2-ynamides should be prepared using catalytic methods, and there are a variety of examples that were reported. Pd/Cu catalyst systems were used for the reaction of carbamoyl chlorides with terminal alkynes;^[4] however, the use of such acid chloride derivatives is undesirable. There are a number of more recent reports exploring catalytic alternatives. Dong et al. demonstrated a catalytic system comprised of bromoalkynes and amines utilising Pd₂(dba)₃, Xphos and Cs₂CO₃ as the catalyst and Co₂(CO)₈ as the carbonyl source (Scheme 1A).^[5] Lee and co-workers reported the use of alkynyl carboxylic acids and amines with CO gas, using Ag₂O as a base and oxidant (Scheme 1B).^[6] Ye and co-workers used a Cu catalyst for the cross dehydrogenative coupling of terminal alkynes with for-

mamides (Scheme 1C).^[7] In this case a large excess of the formamide reagent was required.

Owing to our previous work in Pd^{II} catalytic oxidations,^[8] we were particularly interested in the oxidative carbonylation methods, which use Pd catalysts with O₂ as the oxidant and CO gas as the carbonyl source. In general, Pd-catalysed oxidative carbonylation reactions offer potentially advantageous synthetic methods,^[9] but such reactions have been less well developed compared to other areas of Pd^{II} oxidation chemistry, such as alcohol oxidation.^[10]

We recently developed a system for the synthesis of 2-alkynoates through oxidative carbonylation of alkynes and alcohols.^[11] Moving on from this work, the aim of this study was to improve the synthesis of 2-ynamides. There are a number of previous reports that use alkynes, secondary amines and CO to produce 2-ynamides. This route is desirable because alkynes and amines are commercially available and inexpensive, and these reagents are used without additional functionalisation to activate them. Additionally, CO is an abundant and inexpensive source of the carbonyl group. In 2001, Gabriele et al. reported a method which utilised a simple PdI₂-catalyst system (Scheme 1D).^[12] In a study focused on the preparation of 2-alkynoates (in which the nucleophile is an alcohol), Yamamoto and co-workers showed that their catalyst system (PdCl₂ and triphenylphosphine in DMF) could also be used for the synthesis of 2-ynamides, using diethylamine.^[13] Recently, Xia and co-workers reported a Pd^{II} system with an *N*-heterocyclic carbene ligand (Scheme 1E).^[14] Bhanage and co-workers reported a heterogeneous system that used Pd on carbon in 1,4-dioxane with tetrabutylammonium iodide, [NBu₄]I, as an additive.^[15] Recently, the same group reported the use of Pd on carbon with KI as an additive in acetonitrile.^[16] In this report they utilised tertiary amines (i.e., the reaction involved an *N*-dealkylation step), resulting in the formation of a mixture of products in the case of unsymmetrical amines.

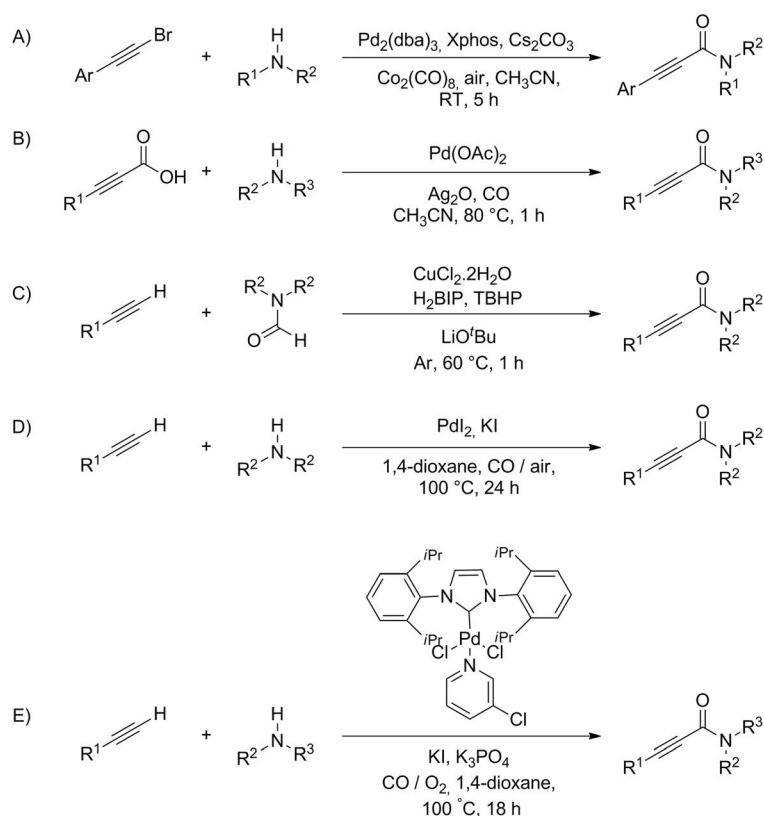
We felt that the work to-date had aspects that needed to be addressed because the reaction conditions would significantly hamper the wider application of these catalytic methods. In particular, the reliance on hazardous solvents is an issue. DMF was used by Yamamoto and co-workers,^[13] whereas the three papers which focussed on 2-ynamide synthesis using secondary amines all employed 1,4-dioxane. Solvents are crucial to the sustainability and safety of chemical reactions, and so it is important when optimising a catalytic method to critically evaluate the solvent selected. Solvent-selection guides, based on safety, health and environment criteria, produced by some of the world's largest pharmaceutical companies, classed DMF

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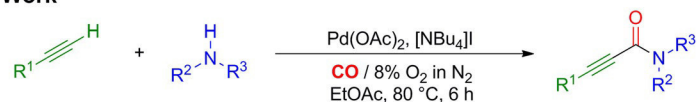
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Previous Literature Examples



This Work

**Scheme 1.** Examples of the synthesis of 2-ynamides.

and 1,4-dioxane as “hazardous” and “problematic” and stated that such solvents should be avoided.^[17] Furthermore, ethereal solvents such as 1,4-dioxane are arguably completely incompatible for performing oxidation reactions in a safe and scalable manner. It is well known that such solvents readily form peroxide species and laboratories have to take precautions if using such solvents in general, for example, only storing them for short periods and testing for the presence of peroxides.^[18] 1,4-Dioxane is often reported in the academic literature as a solvent or co-solvent in oxidation reactions, and it could be that the presence of peroxides is a factor in aiding the reactivity. There are a number of studies on Pd^{II}-catalysed oxidation systems that have investigated the role of peroxides resulting from 1,4-dioxane.^[19] Although such systems may be academically interesting, we believe that the use of ethereal solvents for aerobic oxidation reactions is not something that would be adopted by industry. We believe that the use of such an oxygen sensitive solvent hinders this area of catalysis. In this study we have employed ethyl acetate, which is classed as a “recommended” solvent in the solvent-selection guides developed by the pharmaceutical industry.^[17]

There are additional safety issues for aerobic reactions, and the safe use of O₂ has not been discussed in these previous oxidative carbonylation studies. Although there is no doubt that O₂ is the most economical and sustainable terminal oxidant it does pose safety hazards, particularly if used on a larger scale. The flammability of organic solvents is one important consideration, and employing limiting oxygen concentrations (LOC) is one way to try and use O₂ safely. The LOC of ethyl acetate at 100 °C is 9.4 vol% O₂ at a pressure of 1 bar absolute and 9.9 vol% O₂ at a pressure of 20 bar absolute.^[20] An additional issue with carbonylation reactions is that CO is a flammable gas. The lower flammability limit [LFL, also referred to as the lower explosion limit (LEL)] of carbon monoxide in air is 11.5 vol% at 100 °C and atmospheric pressure.^[21] The upper flammability limit [UFL, or upper explosion limit (UEL)] is 75 vol% at 100 °C and atmospheric pressure. In the case of the method by Gabriele et al. (Scheme 1D), they utilised a gas mixture of CO and air in a 4:1 ratio at a total pressure of 20 atm.^[12] It would appear that this ratio is in-line with the UFL (i.e., the fuel rich region). However, industry would prefer to operate within LFL conditions (fuel lean region). First of all, it is known

that with increasing pressure the LFL values decrease somewhat but UFL values increase and do so to a greater extent.^[22] Additionally, if UFL conditions are used there is an inherent danger because if the vapour phase is vented (or if there is a leak) the gas mixture will pass through the flammable/explosive region as it mixes with the air. If LFL conditions are used the gas will not form ignitable compositions upon mixing with air.^[23] In this study we used 5 bar CO and 30 bar of an O₂/N₂ (8:92) gas mixture. As recently highlighted by Stahl and co-workers,^[20] there is a lack of safety data under the types of reaction conditions that are used in aerobic catalytic reactions; therefore, the conditions we used have not been studied exactly. However, we based our conditions on the aforementioned LOC and LFL data, which should mean the system is safe. Importantly, it also demonstrates that the catalyst can operate effectively under such conditions.

We commenced the reaction optimisation using phenylacetylene and diethylamine as the model reaction in the presence of PdI₂ (0.2 mol%) and [NBu₄]I (2.5 mol%). The reaction was performed at 80 °C in EtOAc for 6 h with a 1:2 ratio of alkyne/amine.

We initially screened both 8% O₂ in N₂ and air (30 bar) with CO (5 bar), finding that both afforded almost identical results. This indicated that the system was not limited in O₂ when operating under these more dilute conditions. This is important because if the system is limited in O₂ Pd⁰ aggregation and catalyst deactivation will occur. Moving on from this, we screened a variety of Pd salts, as shown in Table 1.

The reaction proceeded with all the anions tested; however, the best results were observed with carboxylate anions such as acetate, and pivalate. This contrasts with what we observed in the previous 2-alkynoate studies, with catalyst activity only obtained if carboxylate anions were used.^[11] Acetate has previous-

ly been shown to be a key component in oxidative carbonylation reactions for the synthesis of 2-alkynoates, either as the Pd salt or as an additive in the form of NaOAc.^[13,24] The observation that the 2-ynamide reaction proceeds readily without the presence of carboxylate anions would suggest that the role of the acetate in the 2-alkynoate reactions is for deprotonation of the alcohol; something previously shown in Pd^{II}-catalysed alcohol oxidation reactions.^[25] We also noted the importance of the Pd(OAc)₂ salt purity, something that we also observed in the synthesis of 2-alkynoates. The importance of Pd salt purity and its effect on catalytic performance has been discussed recently,^[26] and we believe it is worth highlighting such factors to aid reproducibility.

Having chosen to utilise Pd(OAc)₂ for the remainder of the studies, we then went on to study the effect of ligands. For the synthesis of 2-alkynoates the system was greatly affected by the presence of ligands and we found optimal performance with tetramethylethylenediamine (TMEDA).^[11] However, in these aminocarbonylation studies we found that ligands (such as TMEDA and phenanthroline) were not necessary and did not lead to any enhanced performance under the conditions studied. It could be that in this case the amine substrate acts as an adequate ligand. The lack of ligand and the loading are very similar to the conditions by Gabriele et al., who used 0.2 mol% PdI₂ (Scheme 1 D).^[12] However, it contrasts the recent work by Xia and co-workers, stating that under their conditions superior performance was obtained if they employed an *N*-heterocyclic carbene ligand (Scheme 1 E) and the catalyst loading was 1 mol%.^[14] We were pleased to discover that we could avoid the use of ligands and higher catalyst loadings, clearly an advantage from both economical and green perspectives.

In many previous reports of Pd oxidative carbonylations, iodide salts were a key ingredient; therefore, we examined the effect of such additives, as shown in Table 2.

Although KI was used by Gabriele et al. (Scheme 1 D)^[12] and Xia and co-workers (Scheme 1 E),^[14] it can be seen that we observed little of the desired 2-ynamide when using KI under our reaction conditions. We presume that the high activity with [NBu₄]I is the result of increased solubility in our chosen reac-

Table 1. Influence of Pd^{II} salts on catalytic performance.

Counterion X ⁻	Conv. alkyne ^[a] [%]	Product yield ^[a] [%]
I ⁻	76	75
Cl ⁻	71	66
F ₃ C-C(=O)O ⁻	77	73
CH ₃ -C(=O)O ⁻	87 ^[b] 77 ^[c]	86 ^[b] 68 ^[c]
(CH ₃) ₃ C-C(=O)O ⁻	86	84
CH ₃ CH ₂ -C(=O)O ⁻	79	73

[a] Conversion and yield were determined by GC using biphenyl as internal standard. All results shown are an average of two experiments.
[b] Pd(OAc)₂ of purity ≥ 99.9%. [c] Pd(OAc)₂ of purity 99%.

Table 2. Effect of additives on the catalytic system.

Additive	Conv. alkyne ^[a] [%]	Product yield ^[a] [%]
–	24	1
[NBu ₄]I	87	86
[NBu ₄]Br	39	22
[NBu ₄][OAc]	9	3
KI	34	1
KI/[NBu ₄][OAc] ^[b]	9	3

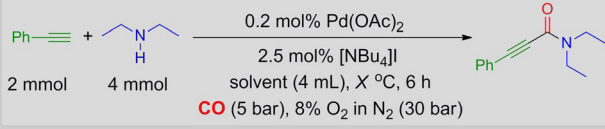
[a] Conversion and yield were determined by GC using biphenyl as internal standard. All results shown are an average of two experiments. [b] 1:1 ratio, 5 mol% overall.

tion solvent, ethyl acetate. We also found the same behaviour with the previously mentioned 2-alkynoate system.^[11] We tested various loadings of [NBu₄]I, comparing 1.25, 2.5 and 5 mol%, to find 2.5 mol% to be the optimum. At present, there is no well-proven explanation or consensus on the importance of such iodide salts in the oxidative carbonylation reactions, and further work is needed to develop a better understanding.

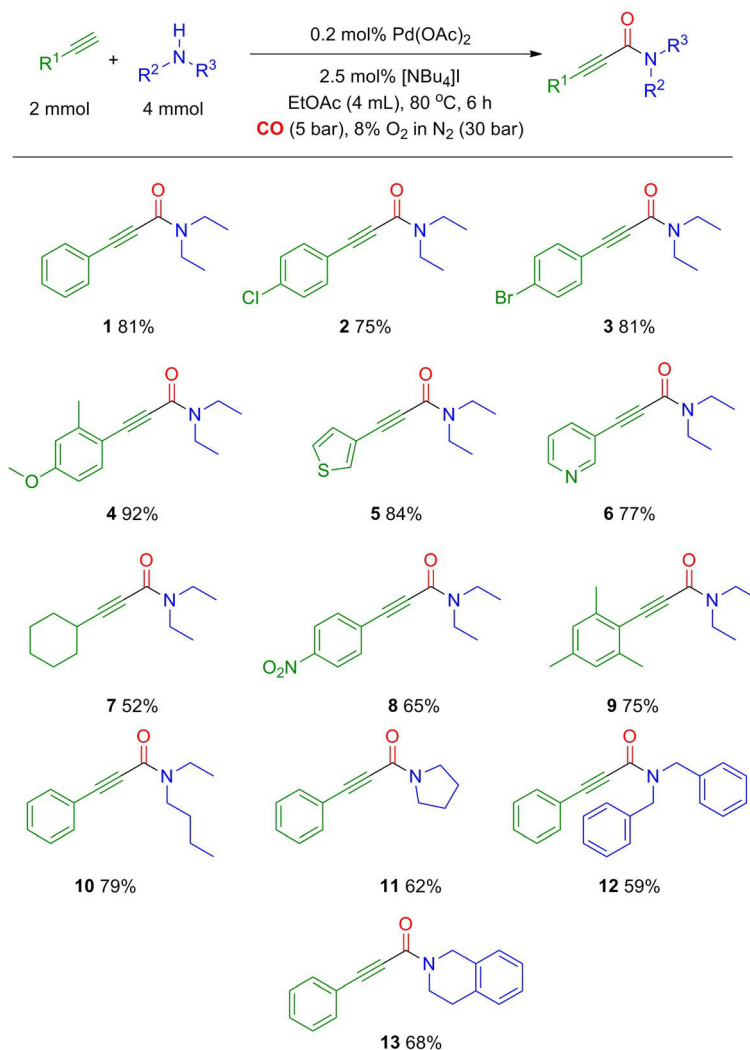
We tested other parameters of the reaction system, including solvent, base and reaction temperature. The results are shown in Table 3.

It was shown that ethyl acetate out-performed even the commonly employed 1,4-dioxane under these conditions (Table 3, entries 2 and 3). K₃PO₄ was used by Xia and co-workers (Scheme 1E);^[14] however, under our conditions we observed that the addition of this base decreased the yield (entry 4). A longer reaction time (entry 7) was also tested; however, the results obtained were almost identical to those after 6 h. We found 80 °C to be the optimal temperature; at 60 °C

Table 3. Comparison of reaction system parameters.

					
Entry	Solvent	Base ^[b]	Temp. [°C]	Conv. alkyne ^[a] [%]	Product yield ^[a] [%]
1	CH ₃ CN	–	80	81	53
2	1,4-dioxane	–	80	75	71
3	EtOAc	–	80	87	86
4	EtOAc	K ₃ PO ₄	80	35	32
5	EtOAc	–	60	44	43
6	EtOAc	–	100	90	84
7 ^[c]	EtOAc	–	80	93	83
8 ^[d]	EtOAc	–	80	52	47

[a] Conversion and yield were determined by GC using biphenyl as internal standard. All results shown are an average of two experiments. [b] 2 equiv. of base were added. [c] Reaction run for 16 h. [d] 1:1 ratio of alkyne/amine.



Scheme 2. Substrate scope utilising various alkynes and amines. Yields reported are isolated yields. Further details are given in the Supporting Information.

the activity was greatly reduced, and 100 °C led to a reduction in selectivity. We compared a substrate ratio of 1:1 (entry 8) but found that this caused a significant drop in product yield.

Once the reaction system had been optimised, we tested the system on a variety of alkynes and amines. The results can be seen in Scheme 2. We were able to use both activated and unactivated alkynes. Alkynes containing both electron-withdrawing and electron-donating substituents worked well. The system was proven to be heteroatom tolerant, as can be seen with **5** and **6**. Sterically hindered alkynes such as 2-ethynyl-1,3,5-trimethylbenzene **9** afforded a good yield.

In conclusion, we have developed a method for the synthesis of 2-ynamides through oxidative carbonylation, which utilises low loadings of Pd^{II} and does not require the use of ligands. Importantly, the method avoids the use of dangerous 1,4-dioxane, which was previously the solvent of choice for these reactions. The use of [NBu₄] enabled us to employ the industrially recommended solvent ethyl acetate. We used O₂ as the terminal oxidant and demonstrated that the catalyst could operate under safer conditions with low O₂ concentrations. These factors are important if we are to hope that such catalytic methods are to be exploited on a larger scale.

Experimental Section

Reactions were performed in 45 mL high-pressure reactors made of Hastelloy C276 and fitted with a safety pressure-relief valve. The reaction mixture was placed in a glass liner equipped with a magnetic stirrer. To the glass liner, [NBu₄] (2.5 mol%, 0.05 mmol, 0.0185 g) and Pd(OAc)₂ (0.2 mol%, 0.004 mmol, 0.0009 g) from a stock solution in ethyl acetate (4 mL) were added. This was followed by the addition of alkyne (2 mmol) and amine (4 mmol). The glass liner was placed in a reactor and then pressurized with 5 bar CO, followed by O₂/N₂ (8:92) to give a total reaction pressure of 35 bar. The reactor was then stirred on a pre-heated heating block at 80 °C for 6 h. Once the reaction was complete, the reactor body was cooled in an ice-bath and then slowly depressurised in a fume hood. The reaction mixture was then poured into a separating funnel, and brine was added. The aqueous layer was separated and back-extracted with ethyl acetate twice. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography, and the appropriate fractions were combined and concentrated under reduced pressure. The product was then dried under high vacuum.

Note: Appropriate safety precautions should be in place when performing these reactions. More experimental details and analytical data are given in the Supporting Information.

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